Harvard Medicine

WINTER 2015

Assembled With Care

Architecture and the healing arts

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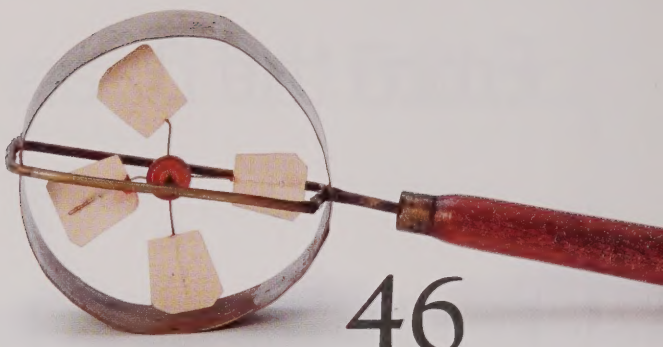

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From the Dean

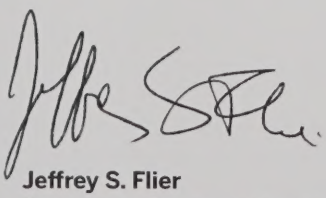
IF, LIKE ME, YOU'VE HAD THE PLEASURE of visiting St. Paul's Cathedral in London, you know it is a stunning achievement. For more than 300 years, it has awed, and served, the people of that city. Its design, and that of dozens of other structures in London, established Christopher Wren as an architect of renown.

Wren may have been among the vanguard of architects who understood what "good bones" brought to architecture. He excelled at structural innovation, including the mathematically precise application of slope, curve, and arch to produce soaring space, like the dome of St. Paul's.

Wren brought this same insight to anatomical illustration years before his success as an architect. His drawings of the human brain were executed with such precision and beauty that they remain at the bedrock of neuroscience. As an illustrator of anatomy, he understood how integral vessels, membranes, tendons, and, yes, bones, are to human form and function. Those of us in clinical and research medicine understand this, too.

In this issue of *Harvard Medicine*, we explore how architecture—structure and design—informs medicine. We investigate the role that protein structures play in our health and well-being, the value that flexible laboratory spaces bring to scientific collaborations, and how the details of hospital design can help patients heal. In addition, we present a playful take on what can result when researchers and engineers create one-of-a-kind research tools, and we cast an artful eye on the wayfinding details that appear in our affiliate hospitals. Looking beyond the tangible, and into a structure fundamental to our work as physicians, we celebrate the bonds formed in relationships, those forged during medical school and nurtured through four decades by a group of alumnae and those that led an alumnus to transform one state's system of health care and medical education.

I hope that this issue's discussion of the good bones that support research, medical care, and physicians will provide you a new perspective on each. I hope, too, that it provides you with some good reading.



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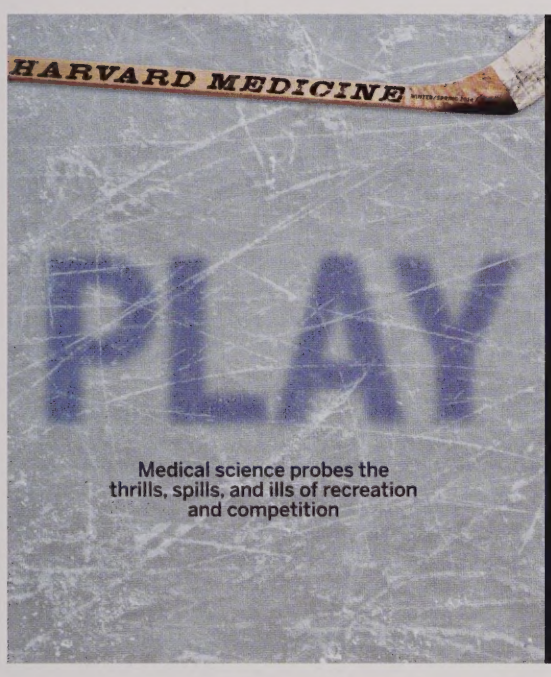
JOHN SOARES

Letters to the Editor

CHART NOTES FROM OUR READERS



In the late 1970s, I was sent from Massachusetts General Hospital to help figure out the cause of a rash that was troubling certain members of the team.

WILLIAM GALLAGHER '60
BANGOR, MAINE

Particle Bored

Reading about the HMS alumni who are physicians to Boston's professional sports teams (*Harvard Medicine* Winter/Spring 2014), I was reminded of my time as dermatologist to the Boston Bruins. In the late 1970s, I was sent from Massachusetts General Hospital to help figure out the cause of a rash that was troubling certain members of the team. It was present in only a few players, and occurred only during hockey season; it gradually cleared in the off-season.

I examined the players in the Boston Garden's locker room. At first, I diagnosed skin conditions that likely were unrelated to the mysterious one I had been invited to identify. One player, for example, had tinea cruris. Another player I saw was a superstar with an extensive case of psoriasiform dermatitis in areas of friction. I found out that during the previous year he had skated in the Stanley Cup playoffs—and had taken large doses of oral steroids!

Undeterred, I examined other players and eventually determined that the eruptions so many were suffering from were the result of contact with fiberglass, which can be both an allergen and an irritant. I learned that the players would shave their fiberglass-wrapped sticks in order to alter the curve in the blade and that they would undertake these modifications to their sticks in a small room while wearing only their underwear. Sure enough, I found fiberglass particles in their underwear and was lucky enough to biopsy one player and find a spicule of fiberglass piercing his epidermis. Ultimately, I found that about ten Bruins had eruptions of varying degrees of severity.

The whole detection and discovery process was complicated by the Bruins' management, which claimed that my findings were skewed and that I was in cahoots with the players in their move to sue the organization for this injury. Suddenly, I was prevented from entering the locker room and from publishing my findings. In addition, I was never paid for my efforts or credited for solving the mystery. Later I was told that other teams had players who suffered from this skin eruption and that after my findings were disseminated throughout the National Hockey League, the players' problem came under excellent control.

Despite these curtailments, I have fond and vivid memories of my time with the Bruins: bringing back to my office bits of Brad Park's underwear to examine them for fiberglass particles, being accepted into the locker room, benefiting from the marvelous cooperation of the players, and my joy at discovering the source of the problem. I learned that they, too, remembered me. One day years later while walking toward the Garden, I ran into the Bruins' former team captain and head coach Terry O'Reilly and his wife. By way of introduction, Terry turned to his wife and said, "This is Dr. Gallagher. He's our dermatologist."

WILLIAM GALLAGHER '60
BANGOR, MAINE

Tickle Me Pink

I enjoyed being a part of the "On Speaking Terms" article in the Summer 2014 issue of *Harvard Medicine*. Although I've always made note of colloquial expressions for diseases or conditions—important if one is to address the complaint correctly—I may now be more attuned to just how surprising these expressions can be. And how they can leave me speechless.

Recently, I was seeing an 81-year-old woman I had taken care of for years. Out of the blue during the examination she asked me, "How is my tickle box?" I had never heard that term, and I was more than a little uncertain about how to respond. After a few awkward moments of silence, the nurse who was in the room with us asked my patient what a tickle box was. The woman looked surprised. "My heart!" she said.

With a great deal of relief, I told her it was normal.

DOUGLAS KELLING '72
CONCORD, NORTH CAROLINA

*Harvard Medicine welcomes letters to the editor. Please send letters by mail (*Harvard Medicine, *107 Avenue Louis Pasteur, Suite 111, Boston, MA 02115); fax (617-432-0446); or email (harvardmedicine@hms.harvard.edu). Letters may be edited for length or clarity.*

Drew Gilpin Faust (from left), Jeffrey S. Flier, and Joshua Boger at the launch of The World Is Waiting: The Campaign for Harvard Medicine

THE WORLD IS WAITING

HMS launches $750 million fund-raising campaign

DISEASES THAT STILL HAVE NO CURE. A critical shortage of primary care practitioners. Health disparities at home and abroad. Questions about the most basic biological processes.

Harvard Medical School researchers, trainees, and students do not lack for potentially transformative ideas of ways to tackle these and other challenges in health care and basic biomedical science.

What is in ever-shrinking supply, however, is funding that can help turn their ideas into solutions.

On November 13, 2014, HMS launched a $750 million fund-raising campaign aimed at helping its research and education community fulfill the School's mission to alleviate human suffering caused by disease.

"There isn't a day that I don't see a proposal on my desk that promises to illuminate our understanding of some fundamental process, or even to save lives," said Jeffrey S. Flier, dean of the faculty of medicine at Harvard University and the Caroline Shields Walker Professor of Medicine, during the campaign launch event at the Boston Park Plaza Hotel. That promise all too often goes unfulfilled, said Flier, because "it probably won't get funded."

"Even at Harvard," he added, "this pulsing ecosystem of energized people able to educate, innovate, and discover, we cannot fund everything we should—and must. Through this campaign, we will use our most effective tools—education, discovery, service, and leadership—to address the greatest health care challenges of our time."

The World Is Waiting: The Campaign for Harvard Medicine is part of the $6.5 billion Harvard Campaign, which launched in fall 2013.

"Tonight, what a privilege it is to glimpse the vast dimensions of medicine at Harvard," said Drew Gilpin Faust, president of Harvard University and the Lincoln Professor of History, in her address to the attendees, "the physicians and the teachers and the discoverers, some 20,000 faculty and students and nearly 10,000 alumni whose new ideas stretch minds and change lives across the world every day."

"Together we can stretch our minds with new ideas and improve human lives," she added.

The campaign supports four priorities:

Education: Training the next generation of leaders in science and medicine by increasing student financial aid, enhancing learning environments, and expanding external education initiatives

Discovery: Illuminating the causes of disease and advancing lifesaving cures by increasing support for biomedical informatics, genetics, neuroscience, systems biology, and the Harvard Program in Therapeutic Science

Service: Building health equity and transforming health systems in the United States and around the world by expanding the work of global health, health care policy, and primary care

Leadership: Incubating innovation and change to improve human health through flexible funding that can be applied when and where it is needed most

The campaign is chaired by Joshua Boger, member of the HMS Board of Fellows and founder and former CEO of Vertex Pharmaceuticals, along with honorary co-chairs Ellen Gordon, president of Tootsie Roll Industries, and Jack Connors, founding partner and chairman emeritus of Hill, Holliday, Connors, Cosmopulos, Inc.

The campaign will conclude in June 2018.

—Stephanie Dutchen

SUZI CAMARATA

The Parts Made Whole

Emergency medicine becomes a full-fledged academic department

THIS PAST FALL, THE HMS COMMUNITY welcomed a new department, the Department of Emergency Medicine. In announcing the change, Jeffrey S. Flier, HMS dean, said, "I hope you share my enthusiasm for the promise this new department holds. I believe it will be transformational, improving emergency medicine clinical care, education, and research in the years ahead."

The change in status, which became effective October 1, 2014, reflects extraordinary collaboration among the hospitals affiliated with the School. These institutions collectively have more than 225 faculty serving as emergency medicine specialists, and feature emergency medicine facilities that can be used for disaster management, toxicology, resuscitation, and the acute care of both medically ill and traumatized patients.

"There may be no better example of the value of emergency medicine," Flier said, "than the response leveraged for the 2013 Boston Marathon bombings, when Boston's hospital emergency departments won well-deserved praise for their outstanding response."

In order to recognize the depth of clinical care, education, and research that exists within the emergency medicine discipline, faculty members, including the chiefs of emergency medicine at the School's affiliated hospitals, have long supported a move to make emergency medicine a distinct academic specialty.

The chairs of the new department are Richard Wolfe at Beth Israel Deaconess Medical Center, David Brown at Massachusetts General Hospital, and Ron Walls at Brigham and Women's Hospital. These three faculty will work together to appoint hospital-based emergency medicine faculty to the new department. Walls, the HMS Neskey Family Professor of Emergency Medicine, will serve for three years as the first chair of the executive committee of emergency medicine.

The creation of the department was unanimously endorsed by an advisory group, the Council of Academic Deans, the Faculty Council, and Harvard University.

—Elizabeth Cooney

STEVE LIPOFSKY

Take a Bow

HMS WELCOMED MEMBERS OF THE CLASS OF 2018 as they began the journey to become physicians. Ranging in age from 20 to 36, the class is made up of 164 students, 49 percent of them women. The students hailed from 33 U.S. states and 16 other countries: Australia, Brazil, Canada, China, France, Greece, India, Israel, Italy, Jamaica, Korea, Mexico, Myanmar, Spain, the United Kingdom, and Zimbabwe.

The class roster includes 56 students who identified themselves as being of Asian origin, including Asian Indian, Burmese, Cambodian, Chinese, Japanese, Korean, Pakistani, Sri Lankan, Taiwanese, Tibetan, and Vietnamese. Another 33 students identified themselves as minorities underrepresented in medicine, a category that includes students who self-identify as black or African American, Hispanic other, Mexican-American, Native American, or Puerto Rican.

PUPPY LOVE

Imaging reveals how mothers' brains respond to photos of kids, canines

IT'S NOT UNCOMMON FOR PEOPLE who have pets to refer to themselves as pet parents. But is that bond truly similar to the one a parent has with a child? To find out, a group of HMS researchers at Massachusetts General Hospital conducted a small study that used fMRI, a form of imaging, to capture the brain activity triggered when participants viewed images of their own children and dogs. The participant cohort? Women, specifically, mothers. The report was published in October 2014 in the online journal *PLOS ONE*.

In order to compare patterns of brain activation involved in the human-pet bond with those elicited by the maternal-child bond, the study enrolled 16 women, each of whom had at least one child aged 2 to 10 years and one pet dog that had been in the household for two years or longer.

Each participant was visited first at home, where she was asked to complete questionnaires regarding her relationships with her child and pet dog. While at the home, the researchers photographed the participant's child and dog.

Each participant then visited the Athinoula A. Martinos Center for Biomedical Imaging at MGH for the fMRI screening. Functional magnetic resonance imaging produces a series of photographs that show changes in blood flow and oxygen levels in specific structures of the brain. Such changes indicate levels of activation in these structures. During the individual imaging sessions, each woman would view photos of her child and dog as well as photos of an unfamiliar child and a dog belonging to a different study participant. After imaging, each participant completed additional assessments and rated several images shown during the session on factors relating to pleasantness and excitement.

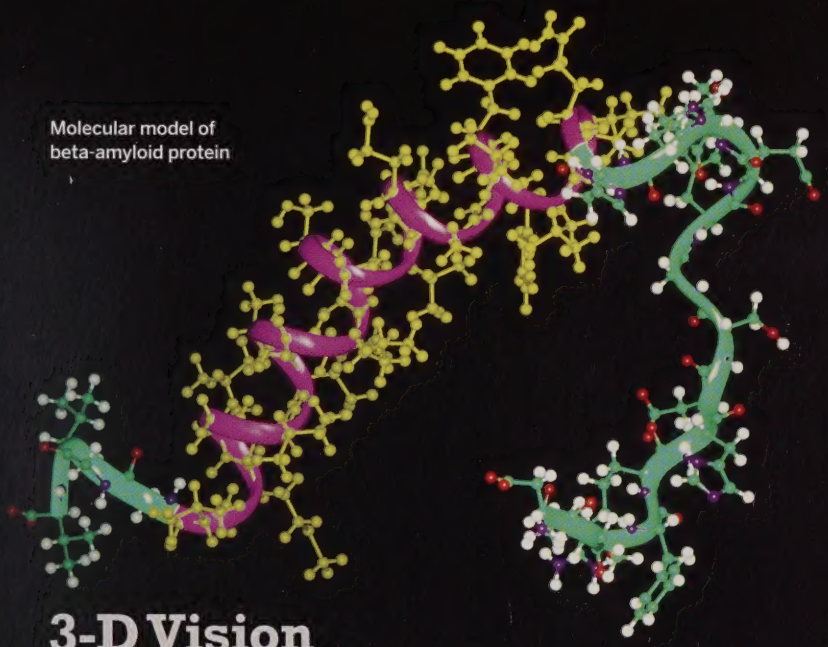
The imaging studies revealed both similarities and differences in the way key regions in a woman's brain reacted to photographs of her child and her dog. Areas reported to be important for functions such as emotion, reward, affiliation, visual processing, and social interaction showed increased activity when a participant viewed images of either her child or her dog.

Images of a participant's child, but not those of her dog, activated the substantia nigra/ventral tegmental area, a region important to bond formation. By contrast, images of a participant's own dog sparked greater activity in the fusiform gyrus, a region involved in facial recognition and other visual processing functions, than did own-child images. The researchers think the greater response of the fusiform gyrus to own-dog images might reflect the increased reliance on visual, rather than verbal, cues in human-animal communications.

The results of this small study, say the researchers, hint not only that a common brain network important for pair-bond formation and maintenance activates when mothers view images of either their child or their dog but also that there may be brain-behavior differences that reflect the distinct evolutionary underpinnings of these relationships.

—*Sue McGreevey*

MATTIAS PALUDI



Molecular model of beta-amyloid protein

3-D Vision

Gel-based system may settle question of how beta-amyloid acts in Alzheimer's disease

RESEARCHERS HAVE SUCCEEDED, for the first time, in developing a laboratory culture system that reproduces the full course of events underlying the development of Alzheimer's disease. Using this system, HMS investigators from the Genetics and Aging Research Unit at Massachusetts General Hospital have provided clear evidence supporting the hypothesis that the deposition of beta-amyloid plaques in the brain is the first step in a cascade leading to the devastating neurodegenerative disease. They also identified the essential role of an enzyme, which, if inhibited, could be a therapeutic target.

"The amyloid hypothesis has maintained that beta-amyloid deposits in the brain set off all subsequent events: the neurofibrillary tangles that choke the insides of neurons, neuronal cell death, and the inflammation leading to a vicious cycle of massive cell death," says Rudolph Tanzi, the Joseph P. and Rose F. Kennedy Professor of Child Neurology and Mental Retardation at HMS, director of the Genetics and Aging Research Unit at Mass General, and co-senior author of the report. The paper appeared in the November 13, 2014 issue of *Nature*.

"One of the biggest questions since then has been whether beta-amyloid actually triggers the formation of the tangles that kill neurons. In this 'Alzheimer's-in-a-dish' system, we've been able to show that amyloid deposition is sufficient to lead to tangles and subsequent cell death."

Genetics and Aging Research Unit investigator Doo Yeon Kim, an HMS assistant professor of neurology at Mass General and co-senior author of the *Nature* paper, realized that the liquid two-dimensional systems usually used to grow cultured cells poorly represent the gelatinous three-dimensional environment within the brain. Instead, the Mass General team used a gel-based, three-dimensional culture system to grow human neural stem cells that carried variants in two genes known to underlie early-onset familial Alzheimer's disease (FAD).

After six weeks, the FAD-variant cells were found to have significant increases in both the typical form of beta-amyloid and the toxic form associated with Alzheimer's. The variant cells also contained neurofibrillary tangles. Blocking formation of amyloid plaques also prevented the formation of the tangles, confirming amyloid's role in the process. The version of tau found in tangles is characterized by the presence of excess phosphate molecules. When the team investigated ways of blocking tau production, they found that inhibiting the action of an enzyme known to phosphorylate tau in human neurons prevented the formation of tau aggregates and tangles even in the presence of abundant beta-amyloid and amyloid plaques.

"This system can be adapted to other neurodegenerative disorders and could revolutionize drug discovery in terms of speed, costs, and physiologic relevance to disease," says Tanzi. "We now can screen hundreds of thousands of drugs in a matter of months without using animals in a system that is considerably more relevant to the events occurring in the brains of patients with Alzheimer's."

—Sue McGreevey

Weak Links

Scientists reveal how penicillin foils bacterial wall building

PENICILLIN, THE WONDER DRUG discovered in 1928, works in ways that remain mysterious nearly a century later. One of the more widely used antibiotics, penicillin attacks enzymes that build the bacterial cell wall, a mesh that surrounds the bacterial membrane and gives the cell its integrity and shape. Once those walls are breached, bacteria die—giving our bodies the opportunity to recover from infection.

That would be the end of the story if resistance to penicillin and other antibiotics hadn't become a serious threat to human health in recent decades. Now, Thomas Bernhardt, an HMS associate professor of microbiology and immunobiology, and his colleagues have added another chapter to the story.

Their findings, published December 4, 2014, in *Cell*, reveal that penicillin deals bacteria a fatal blow by causing the cells' wall-building machinery to malfunction. This malfunction dooms the cell to a futile cycle of building and then immediately destroying that wall. This death spiral depletes cells of the resources they need to survive.

There are two parts to the wall-assembly process: synthesizing strands of linked sugars and then linking them into an expanding matrix. Penicillin and other beta-lactam drugs block enzymes that build cross-links, weakening the wall to the degree that the bacterial cell bursts. The researchers wanted to know what happens after blockage of the cross-linking process to promote the death of the bacterial cell.

To answer this, Bernhardt's team used a derivative of penicillin that targets only one enzyme in cell-wall assembly, and then genetically manipulated a bacterium to make that enzyme nonessential to the cell. To their surprise, the scientists found that targeting the nonessential enzyme with the penicillin still killed the cell. Thus, the enzyme could be removed from a cell without harming it, yet when it was present and bound by the drug, the cell would die.

The investigators found that the drug not only inhibited the enzyme, it also caused it to malfunction. The bacteria made new cell-wall strands, but because linking was blocked, the walls were immediately degraded.

The findings suggest that while a cell has many molecular machines building its wall, antibiotics need to hit some of them to drain resources from the rest.

—Elizabeth Cooney

BACK TO BASICS

Patients who receive advanced life support out-of-hospital have increased risk of death

LIGHTS FLASH, A SIREN WAILS as an ambulance races to help a person whose heart has stopped beating.

In most cases, a 911 dispatcher sends an advanced life support, or ALS, ambulance to the scene, equipped with sophisticated gear and staffed with a crew of trained paramedics who can provide specialized care, including intubations and intravenous interventions.

Unfortunately, according to a study by health policy researchers at HMS and Harvard University, those advanced techniques also increase a patient's risk of death.

People who experience out-of-hospital cardiac arrest and receive ALS en route to the hospital are more likely to die and to have poor neurological outcomes than those treated using basic life support (BLS) techniques, the study finds. The results appear in the December 2014 issue of *JAMA Internal Medicine*.

BLS ambulance crews provide a more limited set of treatments in the field. They provide air to a patient, for example, by using a simple hand-pumped ventilation bag rather than by intubating. BLS crews focus on rapid transport of patients to the nearest emergency department, while ALS providers are trained and directed to provide advanced life support care for cardiac arrest or its accompanying conditions.

"We know that community training, rapid and appropriate delivery of pre-hospital care, and high-quality hospital cardiac care may substantially improve survival rates," says study co-author Alan Zaslavsky, an HMS professor of health care policy. "This study informs the choice between providing more care in the field and bringing patients as quickly as possible to hospital treatment."

For the past several decades, ALS has been the dominant form of care for cardiac arrest and other medical emergencies in the nation, but there is little evidence that it saves lives compared with BLS services. The researchers found that cardiac-arrest patients who received out-of-hospital BLS instead of ALS were more likely to have survived to discharge and were also more likely to have survived 30 to 90 days after discharge. In fact, patients treated with basic life support were nearly 50 percent more likely to have survived than patients who received advanced life support. Hospitalized patients who received basic life support also had better neurological functioning, with fewer incidents of coma, vegetative state, or brain death than patients who had received advanced life support.

For this study, the researchers obtained data from a randomized sample of Medicare claims made by patients in nonrural counties who had used ambulance services for out-of-hospital cardiac arrest between 2009 and 2011. They then compared survival and other outcomes between patients who had received ALS and those who had received BLS. The scientists adjusted for possible sources of bias by studying comparable populations.

—Jake Miller

Mail Service

Doctor-patient messaging meets "meaningful use," but may change doctors' workflow

EMAIL HAS BECOME one of the more widespread forms of communication. With the advent of secure patient web portals and the understanding that online access could improve care, the medical industry is increasing its use of the tool.

While the effect that email exchanges will have on patients and patient care is not yet known, a study from HMS researchers at Beth Israel Deaconess Medical Center offers some insights into its effects on doctors. According to their data, reimbursement models and physician workflow may need to be adjusted to accommodate message management. The results were published online in October 2014 in *Health Affairs*.

"Beth Israel was one of the first hospitals in the country to create a web portal through which patients could securely view parts of their medical records and send emails to their clinicians," says Bradley Crotty '07, an HMS instructor in medicine at Beth Israel Deaconess, a member of the hospital's Division of Clinical Informatics, and the paper's lead author. From 2001 to 2010, nearly 50,000 patients enrolled in the hospital's patient portal, representing about 23 percent of all patients cared for in the system.

During that decade, the researchers found a nearly threefold increase in email traffic between patients and doctors, but that increase appeared not to be the result of individual patients sending more messages but rather of more patients signing on to the portal.

Although patients didn't send more messages over time, Crotty found that some doctors exchanged more emails than others did. Primary care doctors, for example, represented only 50 percent of doctors in the system but received 85 percent of the email traffic.

The federal effort to promote the meaningful use of electronic medical records, administered by the Office of the National Coordinator for Health Information Technology, includes incentives to improve use of patient portals. To receive these incentives, medical providers must meet a threshold of exchanging at least one secure email with 5 percent of their patients within a 90-day window.

Meaningful-use literature cites research demonstrating that secure messaging can help patients adhere to treatment plans, which, in turn, can reduce hospital readmission rates. In their discussion, Crotty and colleagues ask how, in a fee-for-service model of care, doctors would be reimbursed for email time. And as health care moves toward managed-care models, in which email exchanges will likely increase, they question how doctors might better incorporate email exchanges into the flow of their busy work days.

—Kelly Lawman

Closing the Loop

Cause of neural tube defects during diabetic pregnancies discovered

FOR TWO DECADES, scientists have known that the gene *Pax3*, which is required for closure of the neural tube during fetal development, is involved in neural tube defects such as spina bifida. What they hadn't figured out was why that gene malfunctioned during diabetic pregnancies. Fortunately, that mystery has now been cleared up.

A team of researchers led by Mary Loeken, an HMS associate professor of medicine and an investigator in the Islet Cell and Regenerative Biology research section at Joslin Diabetes Center, has discovered a molecular pathway responsible for neural tube defects in diabetic pregnancies. Their findings appear in the October 2014 issue of *Diabetes*.

The neural tube is the body's first step in assembling the spinal cord and the brain; it forms within the first two to four weeks of gestation. A developing embryo carried by a woman with diabetes runs a greater than average risk that its neural tube will fail to close. This failure can result in anencephaly, a fatal disorder, or spina bifida, which can lead to motor impairment and other disabilities.

In previous research, Loeken found that when *Pax3* is exposed to high levels of glucose, it doesn't turn on as often as it should. In this recent work, Loeken describes why. The key is Dnmt3b, a subtype of the enzyme DNA methyltransferase (Dnmt), which adds methyl groups to cytosine, one of the four bases that make up a DNA molecule.

In normal development, Dnmt adds methyl groups to the cytosines around the *Pax3* gene and then tapers off its activity before the *Pax3* gene turns on. But when Dnmt3b is exposed to high levels of glucose, it becomes overactive and causes Dnmt to keep adding methyl groups to the cytosines near the *Pax3* gene. This prevents *Pax3* from turning on—and the neural tube from closing.

Although it would appear that the way to prevent neural tube defects would be to stop Dnmt3b, Loeken cautions against such radical treatment. "This is a tightly regulated process, and Dmnt3b is essential for embryonic survival."

A treatment that may come out of this research is better stem cell therapy. "We might be able to exploit these pathways to make more competent stem cells to repair the congenital malformations," says Loeken.

Neural-tube defects occur in nondiabetic pregnancies as well, affecting about 1,500 births in this nation every year and about 300,000 worldwide. Until a treatment is developed, the best safeguard against complications in diabetic pregnancies, Loeken points out, is to rigidly control the blood glucose levels of women who hope to become pregnant, even before they do.

—Emma Sconyers and Jeff Bright

CATCH OF THE DAY

Twice weekly consumption of fish might prevent or delay acquired hearing loss in women

CONSUMPTION OF TWO OR MORE servings of fish each week could lessen the risk of hearing loss in women, according to HMS researchers at Brigham and Women's Hospital. Their study, which investigated whether the consumption of fatty acids, such as those found in fish, influenced hearing loss in females, was reported in the November 2014 issue of the *American Journal of Clinical Nutrition*. The research team was led by Sharon Curhan '87, an HMS instructor in medicine at Brigham and Women's and part of the hospital's Channing Division of Network Medicine. Gary Curhan '85, an HMS professor of medicine at Brigham and Women's and the Channing Division, is corresponding author.

"Although a decline in hearing is often considered an inevitable aspect of aging," write the authors, "the identification of several potentially modifiable risk factors offers the possibility of preventing or delaying acquired hearing loss."

Although there has been evidence suggesting that a higher intake of fish and long-chain omega-3 fatty acids may decrease the risk of hearing loss, prospective data have been limited. This prospective study looked at links between the total consumption of fish, the consumption of specific types of fish, and the consumption of the long-chain omega-3 fatty acids they contain, and self-reported hearing loss in women. Fish types included shellfish and finfish such as tuna (canned and fresh), salmon, mackerel, cod, and haddock.

Data were taken from the Nurses' Health Study II, an ongoing cohort study that began in 1989. For the Curhans' study, 65,215 women from this group were followed from 1991 to 2009; 11,606 cases of incident hearing loss were reported. When the researchers compared hearing loss in women who rarely consumed fish with that in women who consumed two or more servings of fish per week, they found that the women who regularly ate fish had a 20 percent lower risk of developing hearing loss. When the researchers also looked at the effects of increased consumption of each type of fish, the decrease in risk remained. In addition, a higher intake of the long-chain omega-3 fatty acids in the fish also resulted in a decreased risk of hearing loss.

The findings indicate that the participants' consumption of any type of fish—tuna, dark fish, light fish, or shellfish—tended to be associated with lower risk.

Timed Release

"Decision fatigue" linked to higher rates of prescribing antibiotics

CAN TIME OF DAY affect the treatment decisions of clinicians? According to a study by HMS researchers at Brigham and Women's Hospital, it may, at least when it comes to the frequency with which clinicians prescribe antibiotics.

Clinicians make many patient care decisions each day, and the cumulative demand of these decisions may erode their ability to resist making inappropriate choices. This phenomenon, known as decision fatigue, has been documented in other professionals such as judges. The research team elected to study this phenomenon in medical professionals; their study looked at time of day and the associated rate at which physicians prescribe antibiotics for acute respiratory infections. Their findings indicate that doctors appear to "wear down" during their morning and afternoon clinic sessions and that rates for prescribing antibiotics increase as the sessions progress. The study appeared in the December 2014 issue of *JAMA Internal Medicine*.

"Clinic is very demanding," says lead author Jeffrey Linder, an HMS associate professor of medicine at Brigham and Women's. "In our study we accounted for patient characteristics, the diagnosis, and even the individual doctor, but still found that doctors were more likely to prescribe antibiotics later in the clinic session."

The researchers merged billing and electronic health-record data for patient visits to 23 different primary care practices over the course of 17 months. They then identified visit diagnoses using billing codes and, using the electronic records, identified visit times, antibiotic prescriptions, and chronic illnesses. In all, they analyzed more than 21,000 acute respiratory infection visits by adults that took place during two four-hour sessions, 8 a.m. to noon and 1 p.m. to 5 p.m. The researchers found that the likelihood of prescribing antibiotics increased throughout each morning and afternoon clinic session.

"This corresponds to about 5 percent more patients receiving antibiotics at the end of a clinic session compared to the beginning," says Linder.

Different Drummers

Timing of DNA replication varies among people

WHEN A HUMAN CELL is faced with the task of replicating six billion letters of DNA each time it divides, it doesn't read each chromosome in one slow pass. Instead, its DNA replication machinery divides up the task by beginning work at many origin points. Some segments get copied earlier, some later.

Geneticists at HMS and the Broad Institute of Harvard and MIT have found that this replication plan—including the locations of the origin points and the order in which DNA segments get copied—varies from person to person.

Their study, published in the November 20, 2014, issue of *Cell*, also identifies the first genetic variants that orchestrate replication timing.

"Everyone's cells have a plan for copying the genome. The idea that we don't all have the same plan is surprising and interesting," says Steven McCarroll, an HMS assistant professor of genetics, director of genetics for the Broad's Stanley Center for Psychiatric Research, and senior author of the paper.

"It's a new form of variation that no one had expected," says first author Amnon Koren, postdoctoral fellow at HMS and the Broad.

DNA replication is one of the most fundamental cellular processes. Any variation among people is likely to affect genetic inheritance, including individual disease risk, and even human evolution, the authors say. The study indicates, in fact, that people with different timing programs have different patterns of replication error, which affects mutation risk, across their genomes. McCarroll's team, for example, found that differences in replication timing could explain why some people are more prone than others to certain blood cancers.

"I think this is the first time we can pinpoint genetic influences on replication timing in any organism," says Koren.

Studies that uncover the variations in DNA replication timing—and the potential effects on mutation risk for disease—could flourish now that the team has shown that "all you need to do to study replication timing is grow cells and sequence their DNA, which everyone is doing these days," says Koren. The fast, efficient method could, he adds, "transform the field because we can now do experiments in large scale."

"We found that there is biological information in genome sequence data," adds McCarroll. "But this was still an accidental biological experiment. Now imagine the results when we and others actually design experiments to study this phenomenon."

—Stephanie Dutchen

"How should health care be restructured to better address end-of-life care?"

Perspectives from Atul Gawande and Mildred Solomon

Atul Gawande

There is increasing agreement on a few basics about how we in health care mishandle care not only at the end of life but also for frailty, chronic illness, and other, often inevitable, circumstances of mortal beings. Medicine has failed to recognize that people have priorities besides just living longer—such as the desire to avoid cognitive impairment, to live at home instead of in an institution, to complete major life goals, or to simply be with their dog. The most reliable way to find out what those priorities are is to ask. Living wills rarely spell these matters out sufficiently well to guide care. When conversations about patients' priorities take place, the results are often transformative—providing far clearer direction to clinicians, families, and patients themselves for the many decisions that must be made when quality of life is at risk.

To be most effective, these conversations must be repeated over time (because priorities change), must be respected and communicated to others, and must be valued as a norm. Such conversations also take skill. It is increasingly clear, for instance, that clinicians do not communicate prognoses well and spend too little time asking essential questions such as what their patients' fears and worries for the future are, what their most important goals are, and what tradeoffs they are willing to make—and not willing to make. Professionals need better preparation in these skills. And regardless, patients can, and should, insist that their end-of-life priorities are known and respected.

To make this kind of care happen, a variety of changes are necessary in health care. Medical schools, residencies, and fellowships need to provide teaching in and practice with these basic skills. Health systems should support palliative care departments that not only provide patients with consultations but also provide staff with ongoing coaching

and practice in these skills. Information systems should make it easy for clinicians who meet patients in emergency settings to find documentation about patients' priorities as well as their medical histories. Payment systems should enable physicians to take sufficient time for advance care planning with patients. And we need to actually begin tracking a fundamental measure of the humanity of our care: How many patients feel that their doctors know and respect their priorities in life?

Too often, our debate about end-of-life care is a debate about how people should die. But that is the wrong focus. The goal is not a good death. It is to live as good a life as possible, all the way to the very end.

Atul Gawande '94 is an HMS professor of surgery, a professor in the Department of Health Policy and Management at the Harvard School of Public Health, a surgeon at Brigham and Women's Hospital, and director of Ariadne Labs: A joint center for health systems innovation. He is also the author of Being Mortal: Medicine and What Matters in the End *(Metropolitan Books, 2014).*

Mildred Solomon

Longstanding practice patterns, financial incentives, and our cultural proclivities align to create and maintain systems of care that are failing patients near the end of life. The seriously ill receive poorly coordinated care by numerous specialists, but have no one to help them develop sound goals appropriate to their circumstances. Current Medicare rules incentivize technological interventions but do not cover the high-touch, low-tech logistical and social supports that frail elders need. Cardiopulmonary resuscitation, dialysis, and time in an intensive care unit have become near rites of passage for the dying; for many, these interventions and care settings confer no benefit, and may even be harmful.

Individual clinicians can *ameliorate* these problems by initiating conversations with patients about appropriate goals of care and integrating palliative care consults earlier in the course of treatment. But individual clinicians cannot *fix* these problems. Instead, we must take a systems approach and reset the "defaults."

In most hospitals, for example, the default is that you will receive CPR unless you, or a surrogate, expressly opt out. This approach creates confusion and leads many to insist upon CPR in circumstances where resuscitation attempts are likely not to work, or worse, to cause harm. In a 2012 paper in the *Journal of the American Medical Association*, my colleagues and I called for a new approach that would likely create greater patient and family understanding while reducing the overuse of CPR. Rather than insisting that CPR be the default that patients must opt out of, we urged physicians to assess the ratio of burden to benefit that CPR would likely offer a given patient, and then take one of three approaches: discuss CPR with the patient and family as a plausible option, recommend against CPR, or not offer CPR. Not offering CPR should be explicitly permitted by hospital policy, and the decision to not offer it should be explained to the patient or surrogate.

There are other examples of ways we are practicing care near the end of life that are not in a patient's best interests. Our system currently allows certain nursing home residents—often those with advanced dementia—to be sent to hospitals to have feeding tubes inserted, despite the evidence that feeding tubes do not reduce aspiration pneumonia in this population. These transfers increase health care costs and may exacerbate the dementia. There is also growing evidence that thousands of patients are referred for dialysis without adequate discussion about what it can and cannot do for them. Physician leaders should reach beyond medicine to engage with systems engineers, behavioral economists, nurses with quality improvement experience, and professionals in other disciplines to plan new pathways of care better suited for those in the final phase of life.

Progress must also take place in what we pay for and how. Health care leaders are well positioned to call on Medicare to reconsider its reimbursement priorities. Financial penalties for hospital readmissions may not be welcomed by all, but they can be an impetus for enhanced continuity of care across acute, long-term, and home care settings. Likewise, with accountable care organizations receiving capitated payments for a given population, there is now the incentive to shift from providing more care to providing more appropriate care. Of course, the risk of doing too much could then become the risk of doing too little. We therefore need to monitor such approaches closely to ensure that they bring the benefits they promise, especially for people near the end of life. ■

Mildred Z. Solomon is an HMS clinical professor of anaesthesia at Boston Children's Hospital, director of the fellowship in medical ethics for the School's Center for Bioethics, and president of The Hastings Center in Garrison, New York.

The opinions presented are those of the contributors and do not necessarily reflect those of the President and Fellows of Harvard University or the publishers of Harvard Medicine *magazine.*

TIM LLEWELLYN; COURTESY OF MILDRED SOLOMON (FAR RIGHT)

Mara G. Haseltine
Follicle Stimulator Hormone, 2004
9 x 3 x 3 in
SLS plastic, autobody paint, metal
In the collection of Aliza Eshkhol,
who purified the protein in 1961

The structure of our proteins informs how we function

by Stephanie Dutchen

Strike a Pose

Forget everything you know about cars. You've seen their sleek painted skins but have never peered beneath.

Then your car breaks down. No cell phone signal, no service stations in sight. You stand on the shoulder of the road and stare at your vehicle. How can you figure out what's wrong if you don't know how it worked in the first place?

If you've never watched an engine while it is running smoothly, you'll have trouble figuring out that the drive belt is important and shouldn't be torn. If you don't know that gas tanks hold fuel, you won't consider a hole in the tank to be a problem.

Mechanics know that fixing and maintaining cars requires understanding how the parts function—which goes hand in hand with understanding their structures.

The same is true of our bodies. The proteins that keep us running have specific shapes that allow them to do their jobs. When a protein's cap falls off or its "ignition key" gets bent, healthy processes break down.

Researchers can pop the hood on human biology to learn "the nuts and bolts of all the parts and how they go together," says Michael Eck, an HMS professor of biological chemistry and molecular pharmacology at the Dana-Farber Cancer Institute.

Doing so gives scientists and doctors vital clues about what goes wrong in disease—and how those wrongs might be corrected.

Inner Beauty

"There's an intrinsic beauty in the structures in you," says Stephen Blacklow '88, the Gustavus Adolphus Pfeiffer Professor of Biological Chemistry and Molecular Pharmacology at HMS and chair of the Department of Biological Chemistry and Molecular Pharmacology.

The corkscrews, woven sheets, hairpin curves, and other twists of the amino acids that make up proteins can be beautiful. So can proteins' larger-scale shapes, like the sevenfold symmetry of GroES/GroEL, a molecular chaperone in bacteria that, among other duties, helps proteins fold. It's a favorite of Blacklow's. Another favorite is the coiled coil, which contains as many as seven helical strands wrapped around one another.

"It's so simple, yet one of the more beautiful structures in biology. You can parameterize it mathematically," he says. "It's that perfect."

Since the first protein structures were determined in the 1950s, scientists and artists alike have sought to render them in ways that range from the meticulously reconstructed to the whimsically abstract. A potassium channel becomes a shower of sculpted copper curls. A crystalline form inspires a textile pattern. Researchers who have "solved" structures often decorate their offices with 3-D prints, watercolors, or laser-etched glass cubes that portray a protein's coils and bends.

To these researchers, the aesthetics of the structures can be appreciated together with their function.

Good Form

"Whether it's an automobile engine, a fork, or a protein, function is conferred in large part by structure," says Eck.

Just look at keratins. These spiral-shaped proteins coil around one another to form rope-like bundles that give skin, hair, and nails their strength.

Or consider antibodies. Their "Y" shapes allow them to trap invaders with the tips of their arms and to broadcast alarms with their stems.

When scientists investigated how cells receive messages, they learned that receptors on cell surfaces evolved to form specific shapes that interlock with matching message-bearing

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Julian Voss-Andreae
Hemoglobin, 2007
Stainless steel and glass
Height: 7 ft.
Private collection (Zurich)

chemicals. When researchers examined how DNA is copied, they found that the molecule that reads it has a doughnut shape that allows it to slide along the single-helix strand, letter by letter.

"Visualizing biological machines in detail allows you to formulate a depth of understanding that wouldn't be possible otherwise," says Blacklow.

Many diseases develop as a result of genetic mutations that change the shape of a protein. Normal hemoglobin is a ring of proteins surrounding an iron molecule that binds and releases oxygen. Sickle cell disease arises because a mutation in one of those proteins can collapse the deoxygenated hemoglobin, forming a rod. The result of that single deformity—red blood cells that stick within capillaries and break down prematurely—causes pain and tissue damage and can lead to anemia.

Uncovering the role structural changes play in a given disease helps researchers devise treatment strategies. Knowing how a protein has mutated allows drug researchers to target the delivery of treatments; discovering that subsets of patients with the same disease have differently misshapen proteins allows treatments to be personalized. Similarly, understanding how a mutant protein deviates from the normal form provides insight into how scientists might improve a drug's specificity.

"There's almost a scientific mandate to acquire this understanding to intervene in disease," says Blacklow. "Without it, you're shooting in the dark."

Eck studies mutations in a cell-surface receptor called the epidermal growth factor receptor (EGFR). Mutated EGFR gets stuck in the on position, allowing cells to grow too fast. Eck wants to know how EGFR gets stuck in lung cancer. He also wants to switch it off by developing new EGFR inhibitors. Other EGFR inhibitors have become effective cancer treatments.

What's more, Eck wants to design drugs that block only the mutant receptor. Being able to shut down that version in cancerous tissue opens the way for normal EGFR to keep doing its job in other tissues, including the skin and gastrointestinal tract.

Smile for the Camera

Eck's own job would be easier if he could just snap a photo of normally structured EGFR and another of the receptor when it has mutated.

That option isn't available, at least not yet. Instead, Eck, like other structural biologists in the past century, must rely on available indirect visualization methods.

Topping that list is X-ray crystallography, in which researchers painstakingly coax proteins to dissolve in solution and then to grow into tiny, perfect crystals. Once a crystal has formed, researchers can shoot X-rays through it and use the resulting diffraction pattern to compute the three-dimensional position of every atom inside.

The technique may be laborious and ill suited to fat-soluble proteins, but it's still the one to thank for about 85 percent of what we know about characterized protein structures.

Structures of those proteins that don't reveal themselves with this technique might be puzzled out using nuclear magnetic resonance (NMR), which requires proteins to be dissolved but not crystallized. NMR spectrographs can tell researchers a little bit about a protein's dynamics in addition to its structure. The tool does have a limitation: it works for only small proteins.

Advances in electron microscopy now allow researchers to view large proteins atom by atom, no crystallizing required. It's the closest thing researchers have to snapping a Polaroid of a protein.

"It's the most exciting advance in structural biology in the past decade," says Blacklow.

Appearances Can Deceive

Once researchers think they've solved a structure, they have many ways to check whether their solution is right. If they're concerned that crystallization changed a protein's structure, for example, they can compare that structure to one resolved using NMR. Or they can determine whether their findings successfully predict what happens in an experiment.

Sometimes, researchers intuit that a structure is right because it fits what they know of its function and biochemistry. Other times, scientists can't immediately tell if a structure is right because they don't yet know much about the protein's function.

"Knowing what the object looks like tells you a lot about how it *might* work. It doesn't, however, tell you how it *does* work," says Eck. "If you saw a fork for the first time, you might guess that its tines are good for spearing things. But you wouldn't know for sure until you'd seen them in action."

Shape-shifters

Proteins don't stay still. They shift from one shape to another and back again: on, off, open, closed, bound, free, and myriad less easily defined states.

"There's a lot of motion at that scale," says Andrew Kruse, an HMS assistant professor of biological chemistry and molecular pharmacology.

Each protein assumes a certain number of shapes that are biologically important. The difference between those shapes can be striking, like a ballerina bent in a *plié* compared with one leaping in a *grand jeté*. Or it can be subtle, like the turn of a wrist that allows her partner to take her hand.

Big or small, changes in shape affect what a protein can do, so researchers want to see it dance through all of its poses. They want to know what cues the shifts between poses, or, sometimes, how many of a particular kind of protein strike the same pose at the same time.

Joseph Loparo, an HMS assistant professor of biological chemistry and molecular pharmacology, spends his days reconstructing protein choreography.

"We focus on how you get from one state to the next," he says. "Structural biology is the starting point for us."

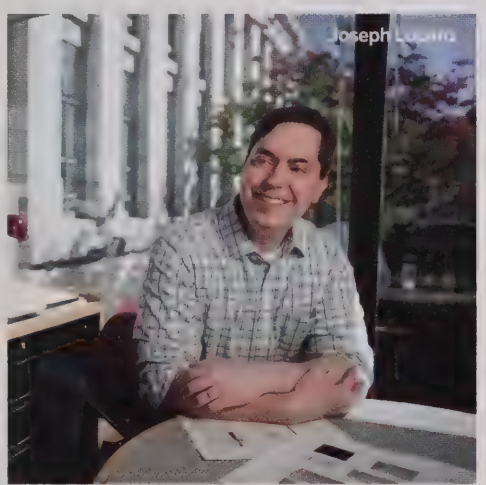
One of Loparo's projects involves protein complexes that repair double-strand DNA breaks. Cells have two ways of repairing such trauma: a careful, error-free way and a quick, slap-dash fix in which the broken ends get jammed back together. Loparo focuses on the latter. He draws on our knowledge of the structures of the complexes to figure out where to attach fluorescent labels to the DNA ends or to the various proteins associated with the repair machinery. Then he watches what happens—in real time.

He hopes what he witnesses will help him answer questions like how a cell "decides when to be really careful and when it can be sloppy" and why the machinery sometimes goes awry. After all, he points out, perfection isn't always advantageous; evolution is a balance between genome preservation and instability.

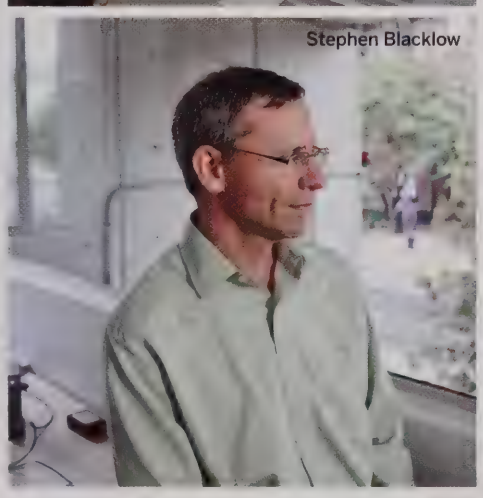
Stuck on You

When describing how proteins work, scientists tend to move their bodies. They might mime graceful helices, open cupped palms like a hinge, or mimic a piston-like motion reminiscent of milking a cow.

When describing how proteins work, scientists tend to move their bodies. They might mime graceful helices, open cupped palms like a hinge, or mimic a piston-like motion reminiscent of milking a cow.


Joseph Loparo


Andrew Kruse


Stephen Blacklow


Michael Eck

When describing proteins in motion, dance becomes a convenient analogy. Eck's students once choreographed an interpretive dance to express how a kinase and a T cell receptor fold together around a zinc atom; the zinc atom was played by a foil-wrapped basketball.

Although individual proteins may resemble elegant dancers, when you cram thousands of them into a cell, each type busting its own moves, the scene resembles more of a mosh pit on fast-forward.

"What's going on in the cell may be closer to chaos than perfectly choreographed movement," says Blacklow.

Performing a dance or making a digital animation may convey that protein dynamics are "really ordered," says Loparo. "But most of what's driving life on this scale is random collision. A lot of bumping into things. You're being thrust about by the crowd around you."

It's unnerving to think that our bodies rely on chance encounters in a rowdy protein crowd. Fortunately, structure helps the right proteins find one another.

Kruse also appreciates how structure contributes to order and function. "Everything is regulated and connected in a way that sets up a balance. Two proteins may collide randomly, but if their structures are complementary, they will stick to each other. And then they can go on to do something useful."

The better matched their structures, the more likely proteins will stick together. Still, it seems a marvel that, more often than not, all this bumping and flailing gives rise to a person's state of health.

"How does any order come from this? That's really what's always been the fascination for me," says Loparo. "These impressive protein machines are given so little to work with and are able to do these complicated tasks accurately."

That's the wonder of evolution, says Blacklow. "Functional demand leads the evolution of shape. The way a protein is structured may not be the only solution, or even the best solution, to an organism's functional need. It may not be what an architect of biology would create. But it does the job. And that's enough." ■

Stephanie Dutchen is a science writer in the HMS Office of Communications and External Relations.

Space Science

Flexible designs give scientists the options needed for collaboration, discovery

by Elizabeth Cooney

CHAIRED SPACE: Researchers in Bernardo Sabatini's neurobiology lab work independently yet have the option—and the opportunity—to share ideas and advice with colleagues.

The scientists and architects huddled deep within one of the century-old structures framing Harvard Medical School's Quad. To one side stood wooden lockers; in a nearby corner, a winding staircase; and in front of the group, a wall. To them, however, it was not just a wall, it was a canvas, one on which they would execute a bold new idea.

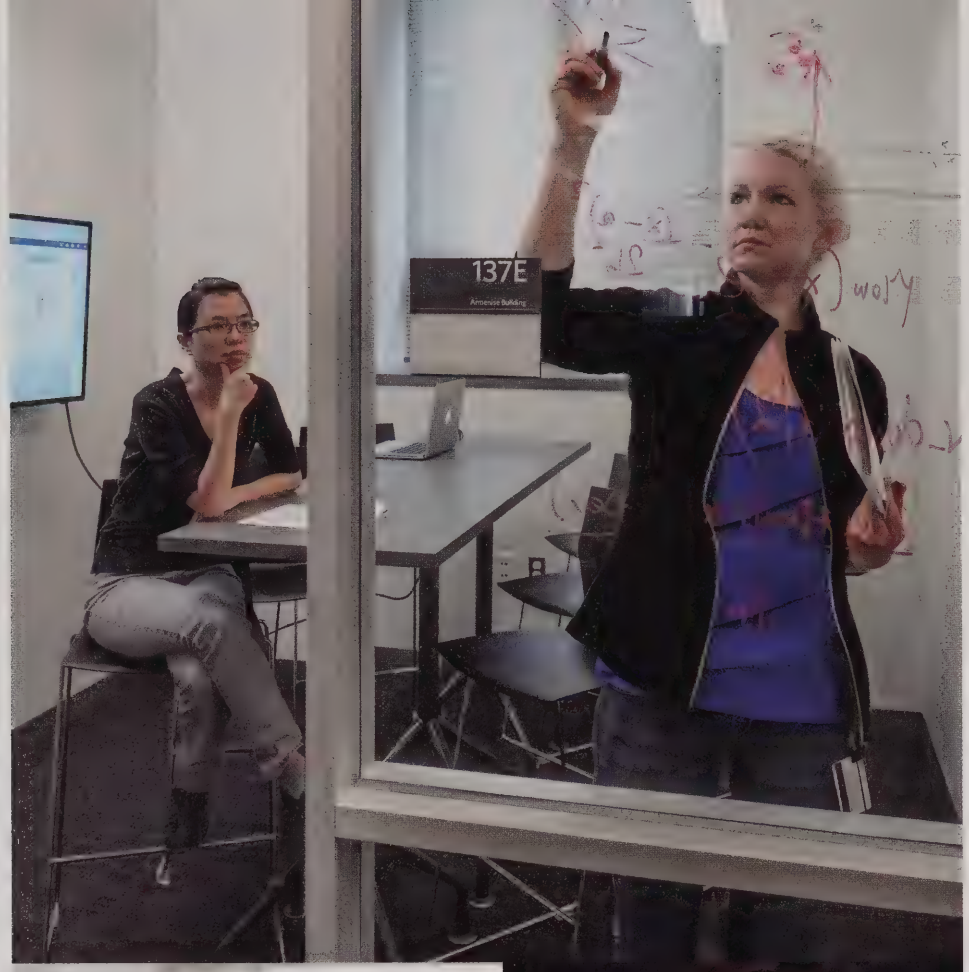
To flip U.S. architect Louis Sullivan's famous phrase, when it comes to designing spaces for discovery, form no longer simply follows function: It defines it. For the past decade, laboratories on the Quad and throughout academia and biotech have been reclaiming the spaces that have tethered solitary scientists to bench and equipment.

Now, laboratories are flexible, capable of accommodating and commingling the scientific pursuits of both individual researchers and research teams. Design fosters collaboration, often incorporating concepts that accommodate the patterns of movement that bring people together—and help propel ideas. The goal, say scientists and architects, is to have laboratory spaces play an active part in shaping what is possible.

These ideas are not new. Jonas Salk, renowned for developing the polio vaccine, saw the value of architectural design as a means for encouraging collaboration and scientific creativity. In the 1960s, he selected noted architect Louis Kahn to give his vision shape. The result, the Salk Institute for Biological Studies in La Jolla, California, features large, open laboratory spaces that are easily adapted to suit changing scientific needs. Salk worked closely with Kahn, urging him to create a facility in which scientific cross-pollination could flourish yet one that was also "worthy of a visit by Picasso."

A half-century later, the National Institutes of Health pegged collaborative science to the biomedical agenda with its 2003 Roadmap, calling attention to the importance of fostering a culture of teamwork in research.

Referencing this intellectual construct, the scientists and architects gathered in front of that blank wall on the Quad contemplated how best to depict the contemporary culture of scientific collaboration. Their interpretation gave rise to a wide glass frontispiece leading to the new Laboratory of Systems Pharmacology. It would, they decided, reflect their mission and their message: You are entering a new place. We invite you to see how we are different.



CHANGING PLACES: Researchers Jia-Yun Chen (seated, top) and Susanne Ramm collaborate in the systems pharmacology lab directed by Laura Maliszewski (above). Neurobiology labs run by Dragana Rogulja and Bernardo Sabatini can be reconfigured as needed.

SHAUN KURRY (TOP); JOHN SOARES

Express Yourself

"We want people who are going to participate in the culture," says Laura Maliszewski, executive director of the Harvard Program in Therapeutic Science, the academic home of the Laboratory of Systems Pharmacology, "not be the lone wolves of traditional research. Participation is the only way you can actually do interdisciplinary research."

Maliszewski is not alone in her thinking on this. A building away, the neurobiology laboratory of Bernardo Sabatini '95 opens wide like a ballroom, with people circling through an airy space bordered with workstations. Rooms dedicated to studying behavior in animals stand apart, while sophisticated equipment is housed centrally or installed within cabinets situated to ease transit as experiments take scientists from one station to another. Discussion spaces cluster in close proximity to Sabatini's office, a welcoming, well-lit space with walls constructed of partially frosted glass meant to define the physical space but not to block the visual field of researchers who are working or simply passing through. A whiteboard displays remnants of the past year's World Cup rankings, silent testimony to the international makeup and interests of Sabatini's research team.

This is the third lab that Sabatini, the HMS Alice and Rodman W. Moorhead III Professor of Neurobiology, has designed at Harvard. He hopes it is built to be his last.

"The key for me was flexibility," he says. "The reason we had to move was simply that we had changed. Our science had evolved."

Sabatini's previous laboratories were fragmented, spread over two floors, with instrumentation crucial to the finely detailed neuroimaging techniques he has pioneered—ultrasensitive microscopes and the 1,500-pound, 4-by-12-foot air tables that cushioned them during use—dominating the space. Using these instruments, Sabatini and his colleagues made breakthroughs that have added to our knowledge of the development and regulation of synapses in the brain and of how they affect behavior and disorders such as autism, Parkinson's disease, and Alzheimer's disease. Not content to work within the limitations of available tools,

Sabatini's team designed new tools for use in their research.

Over time, the scientists expanded their use of animal models and are using highly specialized techniques that are sensitive to light, sound, and smell to investigate the synergistic role that behavior and anatomy have in neurological function. The work has always required collaboration and the sharing of space and instrumentation. Given the directions that discoveries in his laboratory were taking, Sabatini knew that these requirements would only grow. Researchers would need to work in serial spaces—not just a desk/bench combination—and would need to move their work through a range of experiments to achieve breakthroughs.

The new laboratory reflects those needs. "You could think of the modern lab as having many, many workstations that people move through," says Sabatini, "whereas the old design was much more one person sitting at one instrument, essentially all day."

The need to nimbly accommodate discovery proved itself when the paint was barely dry on the new laboratory's walls: space originally designated for refrigerators was reconfigured to hold delicate electrophysiology rigs and fluorescence microscopes.

Susana Zelter, senior laboratory architect at Boston firm Miller Dyer Spears (MDS) and a member of the team that designed the new space, appreciated the reconfiguration on her first visit to Sabatini's lab.

"I was in heaven," Zelter says. "Bernardo had been very clear: He wanted open space, and he wanted it to be flexible. The changes I saw meant the design had satisfied those requirements."

Myron Miller, a principal at MDS, says flexibility is not just a contemporary need. "Any environment has to evolve. A year from now, or five years from now, scientists will have a different way of using it."

Room with a View

A newer member of the faculty, Dragana Rogulja, an HMS assistant professor of neurobiology, studies sleep: why we need it and how we move from waking to sleeping and back again. Her experimental model is the fruit fly, so her lab members spend their working hours in what they refer to as the fly room. Because her team spends so much time there, Rogulja asked the architects to include windows in their design of the room. Like Sabatini, she recognizes that a comfortable environment helps make the long hours demanded by high-caliber research more tolerable—and more conducive to discovery.

The rest of her laboratory is fitted with the light wood casework and dark countertops common in newer lab spaces. Carriers hang from the ceiling, ready to supply power and gases, a configuration of resources that is also common in new research spaces. Rogulja has leveraged the space's flexibility by having the benches spaced to allow for aisles that ease the movements of members of her research team.

"Creating more open space in a laboratory environment breaks down barriers and encourages collaboration," says Robert Quigley, a principal of ARC/Architectural Resources Cambridge, the firm that designed Rogulja's laboratory. "The lab lost about two and a half linear feet in bench space, but she knew the tradeoff was important."

"You give up some space," admits Rogulja, "but it's good for people to be more integrated."

New Twists

Designing flexible laboratory space found its first proponents in the biotech industry. According to Quigley, these companies brought modular design to their workplaces more than two decades ago. The concept gained a greater foothold in academia, he says, as tighter funding made greater efficiency more attractive.

A modular bench unit on concealed wheels can be moved for a fraction of the roughly $80,000 required to shift fixed equipment. Open labs mean fewer walls and fewer doors. Reducing or eliminating the need to tear down and rebuild infrastructure helps lower the costs of setting up new labs and reconfiguring existing ones.

Maliszewski of the systems pharmacology lab says flexibility extends beyond the bench; it also embraces the philosophy underpinning a 2009 report on the so-called new biology. The report was produced for the National Research Council and written by a committee co-chaired by Thomas Connelly of the DuPont Company and Phillip Sharp of MIT.

"The New Biologist," the report says, "is not a scientist who knows a little bit about all disciplines, but a scientist with deep knowledge in one discipline and a 'working fluency' in several."

Work Streams

If there is a tenet fueling Maliszewski's efforts, it might be the belief in the importance of bringing scientists together to learn one another's language. The systems pharmacology laboratory is itself an experiment, mixing together biology, engineering, and medicine in a setting that Maliszewski says provides space for independent discovery.

Her characterization belies her serious intention: Straying from the syllabus to play with new ideas and to collaborate with new colleagues is not only encouraged, it's required. The laboratory intentionally takes students, scientists, clinicians, and computational experts from their "home" or hospital lab and brings them to a light-filled discovery space designed to encourage exchange of ideas and to foster interactions, whether the researchers are on their way to the coffeemaker or to the wet lab.

"The point of the systems pharmacology lab is to take a lot of what systems biology has done, looking at development and genetics and basic biology, and applying them to medicine," Maliszewski says. "This is taking engineering plus biology plus medicine, and sort of squishing them together."

Inside the laboratory, walkways do not run directly from one point to another, thus giving lab members multiple opportunities to interact.

"You have to traverse the corridors, you have to look over people's shoulders, and you have to run into them," Maliszewski says. "It's a huge culture shift—it's team science."

"I've spent a lot of time writing white papers about knowledge transfer," Maliszewski adds. "This is how it happens: Two people sit and talk to each other for more than ten minutes."

It's that simple, and, in a high-powered research environment, that difficult.

According to Jon Whitney, a principal at Janovsky/Hurley Architects Inc., in Wellesley Hills, Massachusetts, the systems pharmacology lab was constructed so that its physical environment could adapt and grow in response to the scientists' continually evolving research.

All three architecture firms are familiar with the constraints posed by the marble buildings erected on the Quad in 1906. MDS, for example, recently opened up the skylight above Gordon Hall's atrium, while ARC has designed lab space at HMS as small as 300 square feet and as large as the New Research Building.

With each assignment, these architects try to imagine the future of science. And as their scientific collaborators are quick to point out, that future will never be a fixed point. Like scientific research itself, laboratory design will always be a work in progress. ■

Elizabeth Cooney is a science writer in the HMS Office of Communications and External Relations.

Fab Lab

Tucked among the Quad's research laboratories is a nexus of inspiration and industry. The Research Instrumentation Core Facility, located along a nondescript hall, can be identified by the one-of-a-kind plaque that hangs at its entrance. That plaque, sporting the School's lion rampant grasping a microscope and calipers and backlit by either blue, purple, or green LED-generated light, hints at the unusual and the unexpected. In short, it gives a visitor an accurate sense of what to expect inside.

Run by Ofer Mazor, an HMS research associate in neurobiology and the facility's senior engineer, and Pavel Gorelik, an HMS staff engineer for research instrumentation, and advised by Rachel Wilson and Bernardo Sabatini '95, professors of neurobiology and faculty liaisons for the facility, the two-year-old facility gives form to concepts. Need a tool that can gently hold steady the head of a fruit fly? They will work with you to get it made. Require a device that will allow cultured neurons to be optically stimulated? They will collaborate with you on sketching out some ideas—then build you the perfect one.

According to Mazor, the facility has few peers among academic institutions; in fact, he and Gorelik often field inquiries from technical personnel at other schools. At HMS, Mazor and Gorelik consult with approximately 70 researchers each year, providing some with advice on turning an idea into an executable design; on developing hardware and software that interface with existing or new instruments; or, using plans they have drafted, on crafting and assembling components for electronic, optical, or mechanical devices tooled to meet the specifications of discovery.

—Ann Marie Menting/photos by John Soares

INVESTIGATOR
Rachel Wilson, professor of neurobiology

DEVICE
Fruit fly behavior arena

FABRICATION DETAIL
Laser-cut plastic sheets

USE
Track animals' responses following stimulation of olfactory neurons


ARCH

INVESTIGATOR

Sandeep (Bob) Datta '04, assistant professor of neurobiology

DEVICE

Olfactory behavior arena for mice

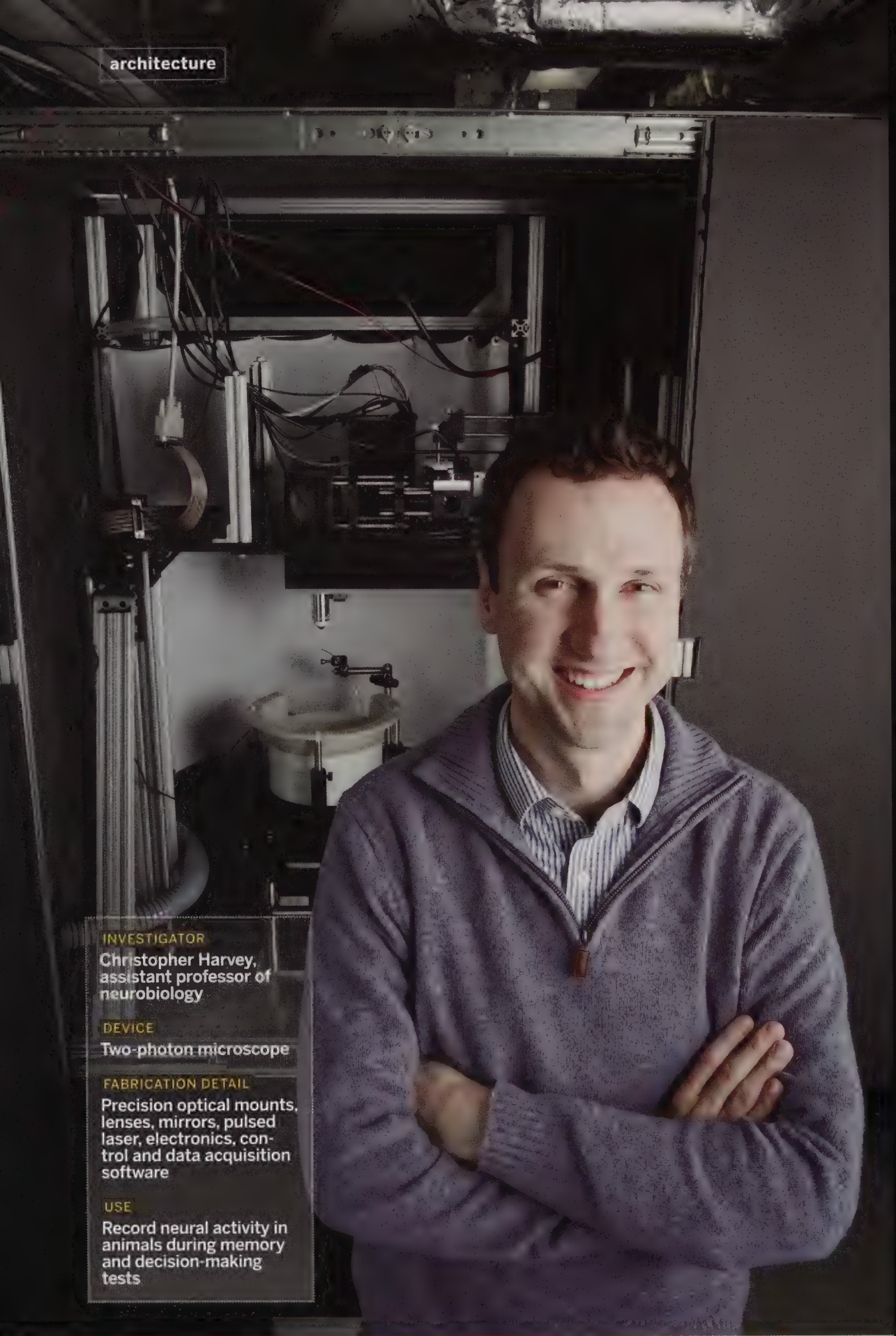
FABRICATION DETAIL

Laser-cut acrylic panels, aluminum framing

USE

Track behavior evoked by animals' exposure to up to four odors


INVESTIGATOR
Jesse Gray, assistant professor of genetics
DEVICE
Optical stimulator for cultured neurons
FABRICATION DETAIL
Ultra-bright LEDs, printed circuit board
USE
Test how neural activity drives changes in gene expression



INVESTIGATOR

Christopher Harvey, assistant professor of neurobiology

DEVICE

Two-photon microscope

FABRICATION DETAIL

Precision optical mounts, lenses, mirrors, pulsed laser, electronics, control and data acquisition software

USE

Record neural activity in animals during memory and decision-making tests

INVESTIGATOR

Rachel Wilson, professor of neurobiology

DEVICE

Fruit fly holder

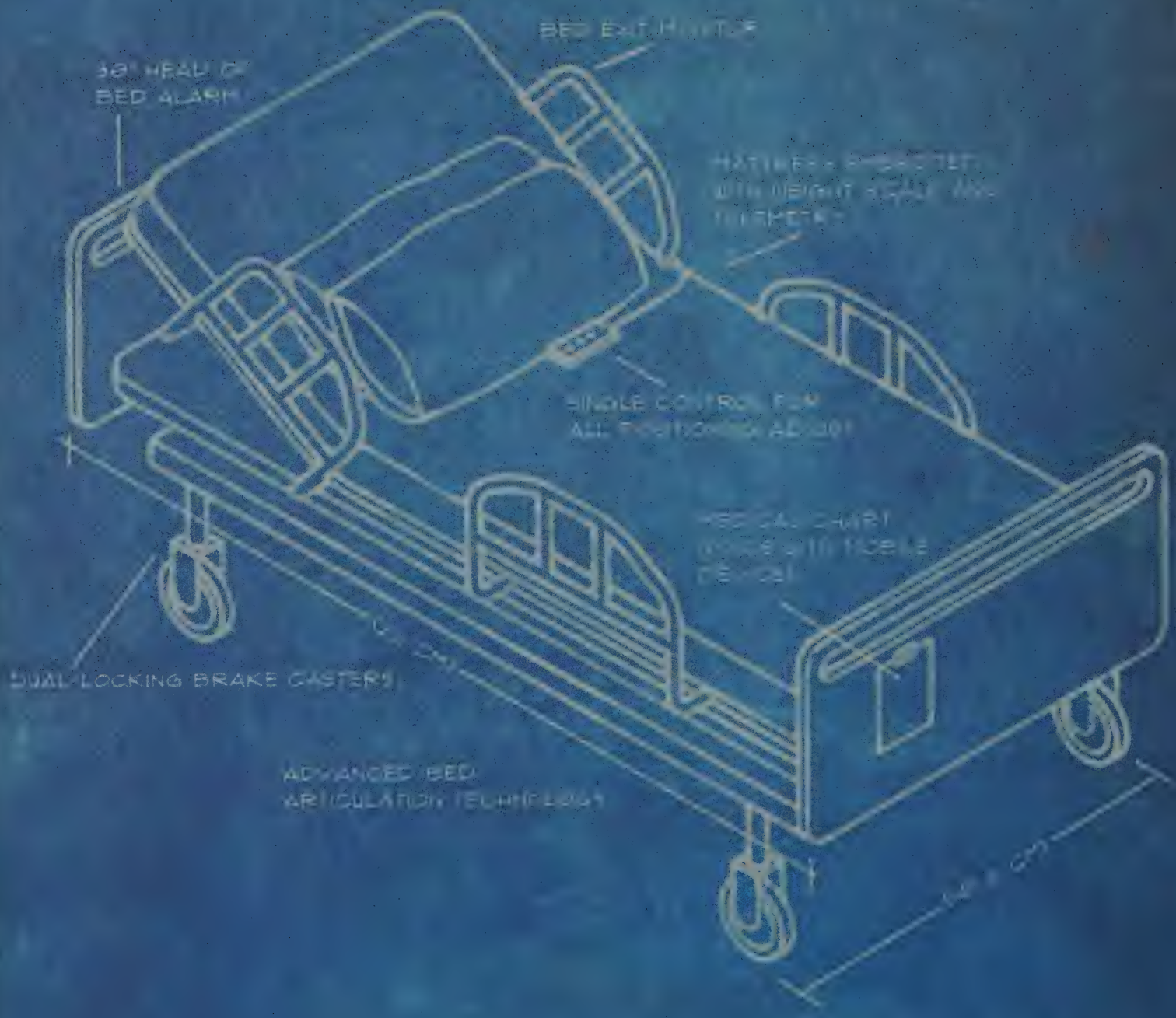
FABRICATION DETAIL

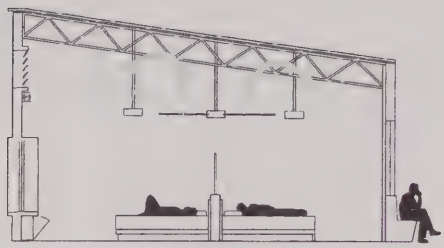
Steel foil precision milled to a thickness of one one-thousandth of an inch

USE

Precise positioning of animal during stimulation and recording of neural activity

SKETCH SHEET





Better by Design

Hospital architecture can help patients heal by Jake Miller

WHEN AN ARCHITECT PLANS a new hospital, she's doing more than designing rooms in which doctors meet sick patients and work to make them well. She's designing a space through which the people, materials, and ideas that drive health care will flow, one that can help patients regain health as it helps maintain the well-being of staff and community alike. Achieving this balance starts with conversations that focus on details and involve caregivers, designers, and patients.

Stephanie Taylor '84, who is a physician and an architect, brings her insights from both professions to the table when she designs a hospital or consults on the planning of one. Her goal: ensure that the buildings are healthy environments for the people who will use them.

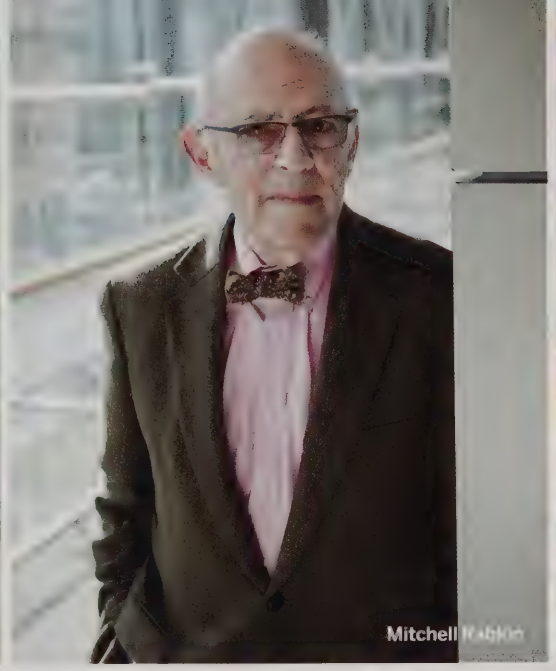
Taylor acknowledges that testing hospital surfaces and air systems for the presence of pathogens is an important part of determining the health of the hospital environment. But she believes that there is an even better way to know whether a building works well.

"You've got the perfect test right in the middle of the room," she says. "It's called the patient."

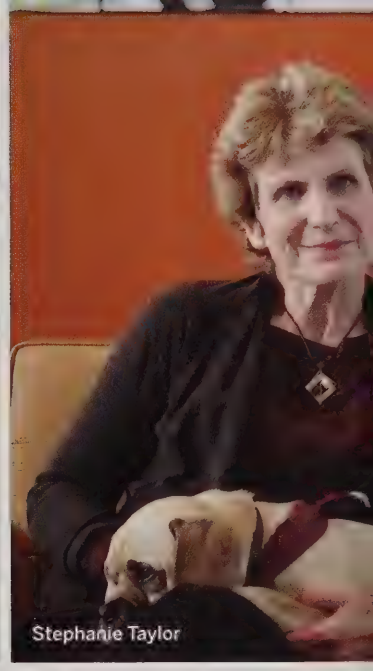
Taylor extends this concept when describing how a building's entire infrastructure functions: Air-conditioning ducts are the respiratory system, while information technology is a kind of neural network that provides sensory data about the hospital's internal environment. Taylor is currently working on projects that overlay engineering schematics on data about patient outcomes to identify whether any particular system—including the movement patterns of staff and visitors—is associated with changes in the rates of hospital-acquired infections or other adverse outcomes.

That Special Touch

Even small design decisions can have noticeable effects. A room with a view of natural spaces—a courtyard garden or a forested mountainside—may sound like a luxury for a hospitalized patient or one visiting a health clinic. Yet clinical studies have shown that the ability to view the outdoors helps reduce stress and improve healing. In one study, patients who recovered from surgery in rooms with windows overlooking natural settings convalesced faster, required less pain medication, and had shorter hospital stays than patients whose rooms had windows that faced a wall. In another study, researchers found that simply being in a room with abundant natural light cut the length of a patient's stay by nearly a third.



Mitchell Rabkin



Stephanie Taylor

Design can also serve the developmental needs of the smallest patients, even if that design calls for nothing more than a comfortable chair in an inviting room.

Hospital architects and doctors are working together to reimagine the design of neonatal intensive care units, moving from wards with many babies and an emphasis on sterility and technology to single-patient rooms that allow for family interaction. Such rooms provide a setting in which parents can spend more time holding their babies, providing the skin-to-skin contact, or kangaroo care, that can have lasting benefits for brain development.

In addition to enhancing neural development, other studies have linked skin-to-skin contact with establishing healthy circadian rhythms and transferring beneficial gut flora from mother to baby. Studies also point to the benefits of spaces in which telemetry alarms are few and interruptions by doctors and nurses are reduced.

"Breaking down old habits, questioning why something is the way it is, that's both the excitement and the challenge of the work," says Martha Rothman, a consulting principal at the architectural firm Shepley Bulfinch. Rothman, who cofounded Rothman Partners, a health care design firm, and who was a founding member and fellow of the American College of Healthcare Architects, has helped hospitals move from traditionally designed neonatal intensive care units to those with environments that better meet the needs of their young patients.

Conceptual Art

Designing a hospital room is a multistep process that, in addition to including conversations among stakeholders, can involve role playing and the development of full-scale models. Rothman notes that it's important that early concepts be roughly sketched, rather than fully rendered: their raw state encourages stakeholders—physicians, hospital administrators, and patients—to think of the sketches as only a starting point for discussion.

Rothman offers an example of the importance of conversations. In the early 2000s when thinking was shifting toward single-infant rooms for intensive care, she recalls, a client's hospital staff was skeptical about whether 80 single-infant units would fit in the space available in their new hospital. When the architects showed the staff what had been achieved in similar projects, the clients' thinking shifted 180 degrees. Rothman says, "They said, 'This is the only way to do it, both for infection control and for parent-child bonding.'"

Age Appropriate

Rothman has also worked on new buildings and renovations for Beth Israel Deaconess Medical Center. Her work on the Shapiro Clinical Center at Beth Israel Deaconess required her to consider the needs of patients who were likely to be non-English speakers or elderly. Her designs allowed for extra space in exam rooms to accommodate family and caregivers, and to allow for privacy during critical medical conversations, such as those that involve interpreters. The extra space can also accommodate attending physicians and medical trainees who visit during rounds.

Although younger patients benefit from the level of infection control that single-patient rooms provide, Mitchell Rabkin '55, Distinguished Institute Scholar at the Shapiro Institute and an HMS professor of medicine, notes that sharing a room may confer cognitive and social benefits on elderly patients that outweigh the advantages of a private room. In addition to the opportunity to interact with another person, sharing a room means twice as many visits from staff and physicians. That's twice as many chances to stay grounded by interacting with people who are not patients, says Rabkin.

For elderly patients, room design can also help prevent delirium. Design components may include rocking chairs and soothing music, artificial or natural illumination that can be varied to reinforce circadian rhythms, and beds that can accommodate spouses and children.

These approaches are all part of the Hospital Elder Life Program, a delirium prevention tool that targets risk factors for the condition. The program, developed by Sharon Inouye, an HMS professor of medicine and the director of the Aging Brain Center at Hebrew SeniorLife, includes room design as a non-pharmacological protocol. Analyses have revealed that good design can help reduce patients' risk of falls, slow their functional decline, and even lessen hospital costs. Design details, even if small, yield considerable benefits: In this country, delirium affects up to 50 percent of hospitalized patients over age 65 at an annual cost of $164 billion.

Little Things Mean a Lot

During his tenure as president of what was then Beth Israel Hospital, Rabkin oversaw the construction of the Feldberg Building, collaborating with the architects, staff nurses, physicians, housekeepers, and others on the design—and on tweaks to the design. In addition to windows that faced the outdoors, the new patient rooms had windows that faced the hospital corridors so that even when the doors were closed for privacy and quiet, patients could see doctors,

OUTSIDE THE BOX: New design ideas have altered all corners of today's hospital, from the neonatal care units at Boston Children's Hospital (far left) to wards that tap the power of a Rwandan community (above) to outdoor spaces that acknowledge the healing touch of nature, like the rooftop garden at Massachusetts General Hospital.

medical students, or other hospital personnel who were about to enter. Conversely, nurses could catch a glimpse inside. Clocks, calendars, and bulletin boards were placed at the foot of the patient bed, rather than at its head, so that the patient could easily view these key points of orientation. Likewise, boards showing the names of the caregivers on duty, the date, and mementos from home helped patients stay oriented to their surroundings and the outside world. These design considerations are prevalent and obvious today, but in the late 1960s when Rabkin was introducing them, they were eye-opening innovations.

When administrators at Spaulding Rehabilitation Hospital began conceptual work for their new building, members of the architectural team spent time navigating the old hospital in wheelchairs to determine what design changes would better serve patients of the rehabilitation facility. In the new building, bathrooms in patient rooms were enlarged to better accommodate wheelchairs; in the former facility, small bathrooms forced many patients in wheelchairs to use shared-access facilities. Patient rooms, once too small for such things as the mechanical aids that people in wheelchairs use to help themselves get in and out of bed independently, were made spacious. And windows, often located at heights that prevented patients in wheelchairs from looking out, were designed to be large, inviting, and accessible to all.

Comfort Zone

Design planning also includes the ever-changing needs of staff.

"You have to think about the nature of the work that people are doing and what they need to be successful," Rabkin says. He recalls that when Beth Israel developed its first intensive care unit, which featured an open nursing station, all rooms were dedicated to patient use. Noting a certain tension among the nurses, Rabkin realized that members of the nursing staff did not have a place where they could safely display their emotions. "Every once in a while, something happens," Rabkin says, "and they just need to chill out a little bit, or weep. You don't want to do that out among the patients."

To solve the problem, a patient room was converted into a staff lounge, a private place to decompress from the emotional burdens of the job. Other changes—sound-dampening materials that reduced noise, spaces lit with abundant natural light—were also made in an effort to help staff provide quality care and to aid staff and patients who are trying to cope with stress.

Ripple Effects

In addition to providing a structure in which to care for patients, hospitals also are a part of the communities that surround them.

One example of the social value of hospitals is a hospital designed by the Boston-based MASS Design Group in the remote Butaro region of Rwanda. The firm's architects worked with local health care providers and community members to assess the medical, physical, and social environments in which they would develop the building. They looked at the project through the eyes of the people who would be using it, an approach that led to what ultimately became a culturally appropriate and medically effective hospital.

In group wards, patient beds are arrayed along centrally positioned walls. The mid-level wall provides patients privacy but also allows staff to see all patients from any vantage point. Each bed includes built-in side tables that preserve the between-patient distance needed for infection control while also leaving room for medical students attending ward rounds.

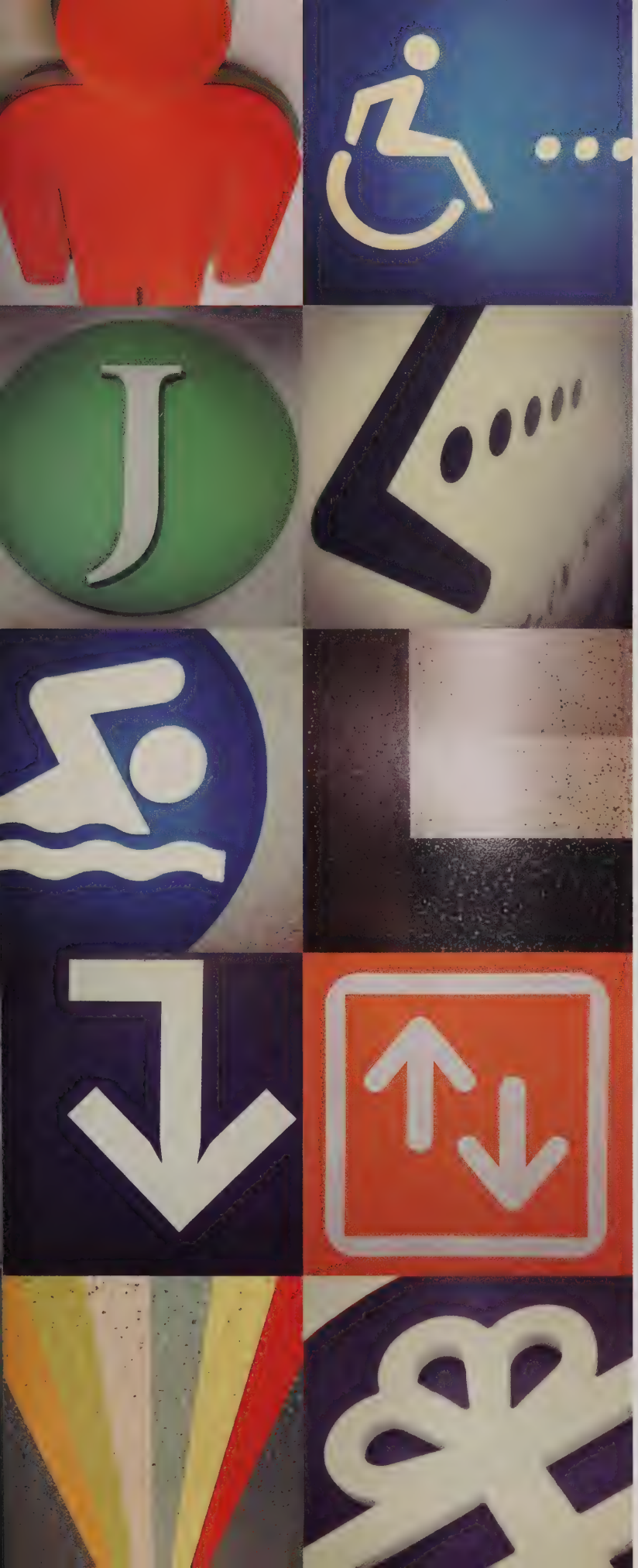
Peter Drobac, who oversaw the construction project as director of Partners In Health in Rwanda, emphasized that it was crucial to think of the hospital as a part of something much bigger.

"We were not building a building, we were building a health system," says Drobac, who is also an HMS instructor in medicine and a physician in Brigham and Women's Hospital's Division of Global Health Equity. The hospital is a hub for a network of community health centers and a crucial driver of economic growth in Rwanda.

Today's hospital designers weigh the needs of those who use and live around the buildings they design. But what ultimately makes a hospital work isn't its walls or windows—it's the conversations, the connections, and the healing that happen inside. ■

Jake Miller is a science writer in the HMS Office of Communications and External Relations.


Find



Way Cool

A HOSPITAL CAN BE INTIMIDATING; it's large, complex, and busy. Yet each day, it will host large numbers of people, many of whom have never entered the building before, some of whom are sick, worried, or both. To help newcomers navigate unfamiliar terrain, architects and administrators have been weaving wayfinding into health care facilities.

Wayfinding cues help people understand where they are, where they need to go, and how to get there. The more noticeable ones involve signage. But other cues can include maps, audio signals, colors, lighting, landscaping, information kiosks, and landmarks such as sculptures and fountains. Wayfinding apps have entered the mix, too.

More elegant cues can also be incorporated into the architecture of new or redesigned facilities. Textures and materials specific to different areas, clear sightlines to elevators and other destinations, and windows placed strategically to allow people to orient themselves using clues from the outside world can all contribute.

Offering wayfinding options increases the chance that there will be at least one that will help each visitor, patient, or staff member. Simplifying or eliminating text helps children, people who have difficulty reading, and those for whom English is not their native language. Other features allow people with cognitive, mobility, sensory, verbal, or other limitations to navigate independently.

Good wayfinding design not only looks pleasing, works intuitively, and communicates universally, it improves people's comfort and confidence. In addition, clinicians can spend less time directing lost souls and more time caring for patients.

"It changes how you feel about yourself," says Cheri Blauwet, an HMS instructor in physical medicine and rehabilitation and director of disability access and awareness at Spaulding Rehabilitation Hospital. "All of these things blend into the flow of your day and your ability to move freely in your environment, whether you're a patient or a physician."

Blauwet, who advised on wayfinding and accessibility for Spaulding's new facility, also uses a wheelchair. Her favorite wayfinding elements at Spaulding are sensors that open doors with the wave of a hand.

"You don't even have to push a button," she says. "It's smooth. Nothing stops you." ■ —*Stephanie Dutchen*


Isfahan


WOMEN
HALF
LESBIAN CONTINGENT

OUR TOWN: The divisiveness of the seventies was felt in Boston and occasionally touched Harvard Yard. The women's group, however, stayed intact and by 1978 had coalesced to ten core members: (back row, from left) Pamela Hartzband, Patricia Williams, Vanessa Haygood, Cathy West, and Anna Fels and (front row, from left) Roberta Isberg, Nancy Rigotti, Susan Okie, and Ourania Malliris. Missing from the photo is Sandy Kopit Cohen.

Structural Integrity

An alliance begun during student days remains strong after four decades

by Ann Marie Menting

July 1975. The first year had ended for the Class of 1978. A three-day weekend lay ahead. It could have been a weekend of relaxation, of catching one's breath after the rigors of preclinical coursework. But it wasn't. In Vanderbilt Hall, one young woman, troubled to a degree unrecognized, ended her life. The tragedy stunned the School's community.

Roberta (Robbie) Apfel, a resident at what was then Beth Israel Hospital, observed the effects that this death had on certain of the women students. Now an HMS associate clinical professor of psychi atry, Apfel had taken a position doing gynecology at the University Health Service during her residency; she had been doing gynecology in North Carolina before coming to Beth Israel.

"A number of the women were unsettled," says Apfel, "in part because it reminded them that they, too, were feeling kind of lonely and down. The transition to medical school had not been an easy one. In college, they had enjoyed close female friendships."

By the time the students returned for second-year studies, the School had a plan of action. Susan Okie '78, a Maryland-based medical writer, recalls: "I think the administration felt that this was perhaps an issue for the women students in particular and that we may not have been receiving enough support."

"So the School supported an effort to start a support group," Okie adds. "An open invitation to attend was sent to the women in our class."

The group of women that gathered for the first meeting winnowed itself over time, and, by the end of the second year, a core group remained. Those women decided to continue to meet as a group. "It provided a sense of belonging," says Apfel.

Today, the group, referred to simply as the women's group, still meets, usually during class reunions. For four decades, the ten HMS alumnae who form the group's core have, according to them, found it to be a source of unconditional support and continuity, a shared expe rience, an island of respect, a community, a touchstone, a sounding board, and a place of trust.

EARLY YEARS: Some of the group's members: (front row, from left) Patricia Williams, Susan Okie, Roberta Isberg, Nancy Rigotti, and facilitator Roberta Apfel and (back row, from left) Cathy West, Vanessa Haygood, and Sandy Kopit Cohen.

ub-bub

In addition to Okie, the group comprises Sandy Kopit Cohen, Anna Fels, Pamela Hartzband, Vanessa Haygood, Roberta Isberg, Ourania Malliris, Nancy Rigotti, Cathy West, and Patricia Williams, all members of the Class of 1978.

Their 165-member class was only the second at HMS to boast a notable number of females: 54. That robust representation mirrored changing times in the nation's culture.

The percentages of females enrolling in medical schools began to swell following World War II. But after the passage of the Civil Rights Act of 1964 and, even more so, after 1970, when a successful class action suit filed by the National Organization for Women compelled compliance with the Act by U.S. medical schools, women began entering in significant numbers. By 1974, when the members of the group entered HMS, enrollment percentages for women had quadrupled from those in the 1950s. At HMS, that growth has continued; the percentage of females in the Class of 2018 hovers near 50—and has for more than a decade.

The city that greeted those ten women was far different from the one that greets HMS women today. In the mid seventies, national politics played out on Boston campuses as the debate over the conflict in Vietnam continued. A court-ordered public school desegregation action, which initiated citywide busing of children, spawned anger, fear, and violence that spilled onto the city's streets, and burrowed deeply into the population's psyche.

The city also was an active hub for gender politics. The limits of the Supreme Court's ruling on Roe v. Wade were being tested in the manslaughter trial of a Boston City Hospital physician who performed early-term abortions. Foreign-language editions of *Our Bodies, Ourselves*, the landmark publication of The Boston Women's Health Book Collective, were being published in Italy and Japan, and the recently formed Combahee River Collective had begun dissecting the oppressive effects of racism and heterosexism, work that would produce the *Combahee River Collective Statement*.

R-E-S-P-E-C-T

Just as Boston's social conventions were being given a vigorous shake, academic traditions at HMS were being tested.

Before coming to Boston, West, an assistant professor in the Department of Primary Care at Touro University College of Osteopathic Medicine in Vallejo, California, had received endless support from her undergraduate colleagues at the University of California, Irvine, as well as from a group of orthopedic surgeons in whose practice she had worked since age 16. "I had done research. I had graduated in three years. As a woman, I felt I had established my credentials. But in lectures there were sexist jokes. The idea that there could be that sort of discrimination, well, it just kind of shocked me."

Says Haygood, an obstetrician-gynecologist in private practice in North Carolina, "There was a sense that the men belonged here and the women were, 'Well, let's just see how it works out.' There was a kind of naturalness to the men's movements that I certainly didn't feel. I felt awkward in that space for a good little while."

Fels, a psychiatrist in private practice in New York City, and a writer, says, "There was a feeling of being anomalous. Various attendings were dismissive. I was at one hospital where they didn't have any jackets that fit women; they were all too big."

Rigotti, an HMS professor of medicine at Massachusetts General Hospital, recalls

COURTESY OF PATRICIA WILLIAMS

a conversation with Isberg. "We were talking about the words we used to describe ourselves," she says. "I remember thinking we needed to start calling ourselves women instead of girls, because we needed to be taken seriously—and because words matter. But," and she laughs lightly, "I also remember thinking, 'I still feel more like a girl than a woman.'"

The feeling of being outsiders was given fresh emphasis each time the women walked the tradition-filled halls of the School. On walls everywhere were portraits of men. Only men.

Lives, Examined

Within their group the women worked through both the difficult and the delightful aspects of life in medical school—and of life in general. The value of peer-support groups such as theirs may be found in the understanding that positive relationships with trusted individuals can boost confidence and serve as a buffer against shared stresses and adversities. As Haygood puts it, "There's just always been a very caring, listening ear available to each of us."

Isberg, an HMS assistant clinical professor of psychiatry at Boston Children's Hospital, remembers the questions considered during the group's early years. "How were we going to figure out how to do this? How could we have a life that was dedicated, at that moment, to studying and learning, but also to working very hard, to having other interests and, one day, to having families? We wanted to know how we could have full lives."

Prosaic issues were tackled by the group, such as how to help two members work through a housing rearrangement in a manner that would preserve their friendship and the group's harmony. So were challenges that were rending society, such as the hostile environments women were confronting at home and in the workplace. Sexist comments, lobbed during lectures or outside dorm rooms, shook the women. They analyzed and parsed the insults, and then moved forward, if not with tools to overcome, then at least with the confidence that the indignities were not theirs alone to suffer.

Perhaps at no time was sororal support more needed, and tested, than when Haygood's presence, and that of other African American members of the class, was challenged by a member of the School's faculty. In a May 1976 issue of the *New England Journal of Medicine*, a noted microbiology professor and HMS alumnus argued that the academic standards of the nation's medical schools had, according to coverage in the *New York Times*, "dropped because of the admission of many minority students with substandard academic qualifications." News of the *NEJM* paper burned through the School. Haygood says, "As this was festering, we had a meeting of our group. We went through many things, but nobody said anything about the paper. So I said, 'You know what? There's something going on here that affects me tremendously, and nobody has said anything about it.'"

The feeling of being outsiders was given fresh emphasis each time the women walked the tradition-filled halls of the School. On walls everywhere were portraits of men. Only men.

Reactions to Haygood's statement elicited a range of reponses: "We didn't bring it up because we didn't want it to be hurtful to you." "We didn't want to dwell on its negativity." "We didn't want to give it life." Haygood explained that she needed to talk about the situation with them because, outside that circle, there were many people who judged and attacked her without knowing her. "I told them I needed them to shore me up so that I could go out and meet all those people—and not react to them by believing what they said."

Okie, too, recalls the circumstance and its lesson. "Because of our group, I remember becoming attuned to learning more about exactly how those claims made one of my friends feel."

The importance of the individual remains a point of pride with the group. "We're not little cookie-cutter, identical types," says Malliris, a pediatrician in the Seattle-based Ballard Pediatric Clinic.

Says Fels, "I think that because we were inventing lives in ways that men didn't have to—cultural roles, family roles, professional roles—our careers have been more inventive and diverse."

"Everybody's story continues," adds Malliris, "our lives have common themes—having children, not having children, being married, not being married, having aged parents, dying parents, sick parents—that are expressed differently because of our life choices."

The experiences from their professional lives are also shared. Says West, "A big part of our group, for me, is the pleasure we take, the really intense pleasure we take, in something that someone does. When we get together and hear about each others' lives, it enriches all of us."

Time Travel

The 1970s may have been an opportune time for such a group to coalesce, and the manner in which it formed, then functioned, may have been critical to its success.

Says Hartzband, an HMS assistant professor of medicine at Beth Israel Deaconess, "Women's lib was an active sort of social construct of the time. We saw ourselves as forging new territory. We were women professionals who were going down a path that not many others had followed. As a group, we really came together."

Williams, who, in addition to being an adjunct professor at American University, works as a consultant in organizational development and training, a role that includes leadership training and coaching, says, "Having a facilitator early on was critical to building a healthy and robust dynamic for the group. When Robbie stepped back as leader we were a pretty healthy group and could continue on our own."

Cohen, who is a clinical assistant professor of psychiatry at Weill Cornell Medical College and firmly associated with the Academy of Organizational and Occupational Psychiatry, would agree. "There's an important ritual to structure; having a facilitator was important to giving a formal nature to our group. It was structured to keep going, even if individuals couldn't come at one time or another. It continued to feel like a group."

"The fact that the group has stayed together has surprised and delighted me," says Apfel. "Its value to all of the women has been repeatedly demonstrated. These women know the importance of touch, a vanishing commodity in medicine these days, and of keeping in touch. Of connection. Of support. Of understanding. The group has given them all strength as individuals."

The Class of 1978 will gather again in 2018 for a reunion. No doubt, so will the members of the women's group. ■

Ann Marie Menting is editor of Harvard Medicine *magazine.*

stately renovation

A life built on public service transformed a state's health care system

by Elliott Miller

To his friends and colleagues, Karl Wegner '58 was a man of resolute purpose. He wanted to make a difference, and he did so by changing and improving health care and medical education in South Dakota. »

NEW FACES: The Sanford School of Medicine in South Dakota, which began as a two-year school (above right), has become a vibrant center for medical care and education.

COURTESY OF THE UNIVERSITY OF SOUTH DAKOTA SANFORD SCHOOL OF MEDICINE (ABOVE AND BELOW, FAR LEFT); COURTESY OF THE WEGNER FAMILY

That drive to make a difference was cultivated from an early age. When just a boy, Wegner would enjoy summers at his grandparents' cabin in the Black Hills of South Dakota. There, he would spend time with his grandfather, Peter Norbeck. Norbeck was a larger-than-life figure—successful businessman, governor, state senator, and three-term U.S. senator—a man with a mind to improve South Dakota and a dream of preserving the state's and the nation's natural beauty. He accomplished both. Norbeck's work helped create Custer State Park in South Dakota and the Wind Cave and the Badlands national parks. Another dream, to transform the open granite faces in the Black Hills into a monument, led to Mount Rushmore.

Norbeck left these considerable legacies to Wegner and to the people of the nation. It's not surprising, then, that when it came to ideas, his grandson thought big. Wegner was determined to improve health care for the people of South Dakota and, in doing so, achieved what he considered to be his greatest accomplishment: transforming a two-year medical school into a degree-granting four-year institution known today as the University of South Dakota Sanford School of Medicine. Located in Sioux Falls and Vermillion, the school emphasizes primary care and family medicine.

ACORNS TO OAKS: Standing tall, first as a youngster (top, right), then as the man behind South Dakota Governor Richard Kneip during the signing of the authorization for a four-year medical school, Wegner devoted himself to improving health care in his home state of South Dakota.

Base of Operations

During his undergraduate years at Yale University, Wegner had focused on engineering but had also gathered credits valid toward a medical school application. Following graduation, he enlisted in the U.S. Marine Corps and was about to join the conflict in Korea when command officers decided his engineering skills would be better used stateside.

By the time he received his discharge, Wegner had decided to attend medical school. In an odd twist of fate, he was denied acceptance into South Dakota's two-year institution; HMS thought otherwise, however, and accepted him. He began his studies in September 1954. During his first year, Wegner developed strong friendships with his dissecting mates in anatomy, Angelo Erakli '58, Sergei Sorokin '58, and Kirby von Kessler '58. Coincidentally, von Kessler also had a connection to South Dakota. He had spent his early years around Fort Meade, the Army base where his father, Major Wilson C. von Kessler, was commander and a surgeon.

In 1962, following a pathology residency at Massachusetts General Hospital, Wegner listened to his heart and returned to South Dakota, accepting a position as chief of pathology at Sioux Valley Hospital in Sioux Falls, then a city of more than 65,000 people. He also began teaching pathology to second-year medical students at the University of South Dakota's two-year medical school. In a few years, this one teaching opportunity put Wegner, and South Dakota's two-year medical school, on a path toward change.

Our Man in Sioux Falls

Wegner's skills as a teacher and as a pathologist were well recognized. So too was his passion for improving opportunities for a medical education in South Dakota. He was encouraged to become dean of the medical school and accepted on the condition that he be allowed to develop the school into a four-year institution with degree-granting authority. It was a change that was sorely needed.

Not only had it become increasingly difficult to place second-year medical students in third-year classes at other schools around the country, but those students often took their residency training where they earned their medical degree. Most never returned to South Dakota. This migration was taking a toll. In the early 1970s, South Dakota had a low, arguably the lowest, physician to population ratio in the United States.

Despite what these facts meant for the quality of health care for state residents, the frugal members of the South Dakota legislature, as well as many physicians in the state, remained unconvinced of the need for change. Many practitioners feared competition and thought it unnecessary to increase the state's number of doctors. They also argued that the state's small population would provide an inadequate training ground for medical students, that they would not gain experience treating a wide variety of disease states.

Wegner focused his efforts on the state's legislators, believing that the physicians would recognize the benefit over time.

"He had to convince a conservative legislature," says Lawrence Piersol, judge of the U.S. District Court for the District of South Dakota and former majority leader of the South Dakota House of Representatives. "He knew South Dakota, and he understood those legislators. I think he saw every one of them and talked to every one of them. And he convinced them."

Adds Piersol, "When I was majority leader, Karl was the person who more than anybody, in my opinion, was responsible for making me and my colleagues believe that we could go from the two-year medical school we had to a four-year medical school. And that it would work. I mean, he worked on that issue without fatigue, and his arguments were credible."

Wegner's education at Yale and Harvard contributed to that credibility, as did having a grandfather important to South Dakota. But serendipity may have occasionally played a role. During a conversation with Kirby von Kessler, Wegner recalled talking with a state senator about his experience in medical school and mentioned that the father of one of his classmates was Major von Kessler of Fort Meade. Kirby von Kessler remembers Wegner saying, "The senator was surprised and said, 'Von Kessler? When I was a child, Major von Kessler took out my appendix and saved my life. He was the only physician for miles around. He charged my parents only $25.'

"Then he asked, 'How much money would you need for that school?'"

Party Politics

There were others who needed to be won over, however. Wegner traveled, calling on people at their homes and places of work. He and his wife, Mary Jo, hosted dinner parties at which he presented his case for the school. During these get-togethers, Wegner would offer novel approaches to overcoming some of the concerns their guests expressed. He countered worries over the cost of construction, for example, by proposing what he called a "medical school without walls" that would use existing health care facilities in Sioux Falls and Yankton, South Dakota, for teaching the final two clinical years.

His efforts were met with success. In 1974, authority was granted by the state legislature with the senate voting 35 to 0 and the house 54 to 14 to establish a four-year degree-granting medical school. Then-governor Richard Kneip also strongly endorsed the change.

"It was really Karl's work—traveling all over the state, talking to everybody—that I think led the legislature to decide to fund a four-year program rather than to close the school," says Robert Talley, former dean of the University of South Dakota Sanford School of Medicine, now with the Sioux Falls VA Health Center. "I really think he carried the day, because when you talked to individuals, they all thought the school would close, and not because South Dakota didn't have the money. Most thought the state wasn't capable of having a medical school. Karl convinced them otherwise."

Family Affair

With the first third-year class entering in 1975 and a four-year curriculum to implement, the new school needed new faculty. Again, Wegner and his wife opened their home to candidates. Their children, Madeleine (Maddy), Mary Nell, and Peter, who had previously distributed bumper stickers promoting the idea of the four-year school, and had even stuck them on their desks at school, were again enlisted, this time to meet with the children of the candidates and to tell them how good it was to live in South Dakota. Taken together, his tactics worked; Wegner assembled a top-flight faculty. Students, too, came to the school, not only from South Dakota but from nearby states as well.

"He changed South Dakota medicine overnight," says John Barlow '58, a retired pathologist who was a friend and colleague of Wegner's. "It just changed. People started to come here."

Transformation

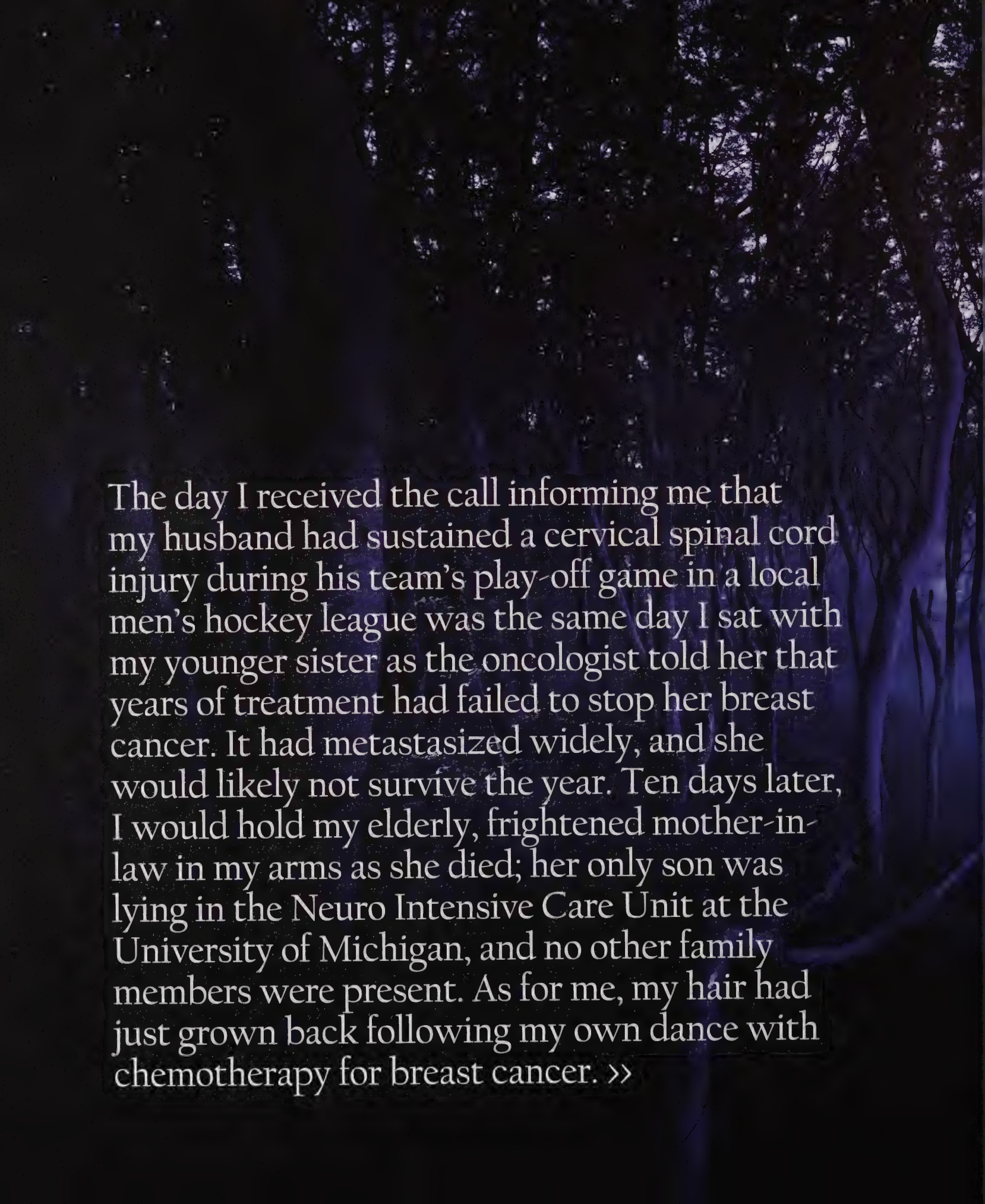
Wegner retired as dean in 1980 and was soon invited to join the Board of Regents, which had responsibility for all colleges and universities in the state. He ultimately became the board's chairman and used his time in the position to promote the development and implementation of quality programming for the students of South Dakota.

The new four-year medical school produced profound changes in Sioux Falls and the state. In the 1960s, Sioux Valley Hospital had 300 beds, as did McKennan Hospital; the Veterans Hospital had 150. Today, there are about 1,200 beds in Sioux Falls' hospitals, and health care has become a significant contributor to the state's economy. The Sanford School of Medicine health care system now serves people living within 200,000 square miles.

Today, South Dakota's medical school stands as witness to Wegner's vision of a competitive, rigorous medical education that would build a corps of homegrown physicians for the state. As noted in the school's mission statement: "The curriculum is to be established to encourage graduates to serve people living in the medically underserved areas of South Dakota." In 2014, 53 new physicians, many of them from South Dakota, received their degrees; more than 600 graduates currently serve the state's population. Outside of education, the medical school has stimulated growth of the biotech and biomedical industries in South Dakota, growth of the state as a regional health care center, and growth of biomedical research in the state.

This past year, Wegner died of complications from a fall. He is, however, remembered well by his classmates. Howard Corwin '58, notes, "In many ways our past and present graduating doctors are the Renaissance men and women of our day, broad in the arts and the sciences, qualified to create and fulfill missions that will benefit humanity. Karl Wegner was one such person. He fulfilled the highest ideals of our noble profession." ■

Elliott Miller '58 has retired from practice and now lives in Maine. Like Karl Wegner, he is a native son of South Dakota.



The day I received the call informing me that my husband had sustained a cervical spinal cord injury during his team's play-off game in a local men's hockey league was the same day I sat with my younger sister as the oncologist told her that years of treatment had failed to stop her breast cancer. It had metastasized widely, and she would likely not survive the year. Ten days later, I would hold my elderly, frightened mother-in-law in my arms as she died; her only son was lying in the Neuro Intensive Care Unit at the University of Michigan, and no other family members were present. As for me, my hair had just grown back following my own dance with chemotherapy for breast cancer. ››

Time Lapse

Upheavals left a physician sadder and wiser, but also made her a better doctor

by Rosalie Tocco-Bradley

That year, 2010, changed me for better and for worse. Better: I believe I became a more aware and empathetic physician. Worse: Losing my sister Maria was heartbreaking beyond consolation, not just for me, but also for the devoted husband and the 11- and 16-year-old children she left behind. Better: My husband, Brian, and I learned to navigate through his rehabilitation and the emotional challenges associated with a life-changing injury. Worse: My mother-in-law died without seeing her beloved son one last time. Better: I'm still here, although I can assure you, there is survivor guilt when your little sister is the one who dies first.

Although I would never wish pain and suffering on a physician colleague, I can tell you that hardship has provided me with perspective, empathy, and wisdom beyond anything I gained in medical school or on grand rounds. In 2008, in the calm before the storm, I thought I was a pretty good doctor. I loved what I did, I worked at keeping current with advances in anesthesiology, and I felt I was able to connect well with my patients. But after my year of heartache, I realized I really hadn't known what personal anguish a patient experiences, or for that matter, the stress that family members undergo when their loved ones are ill or dying.

Family Physician

Let me step back and provide a little perspective on my road to medicine. According to family and tradition, I wasn't supposed to become a doctor. As the eldest daughter in a highly traditional Sicilian family, I was expected to marry young—and to marry Sicilian. I'm not kidding. How many of your parents were disappointed that you chose a career in medicine over a career as a housewife? Thankfully, mine got over their disappointment and even came to respect my decision. It soon became clear that, as the only physician in a family of eight siblings, I had the responsibility of caring not only for my patients but also for my family. This, then, was the point of departure for my professional and personal journeys.

Necessary Evil

Pain and suffering, even that experienced by loved ones, wears you down. Before we learned of my sister's diagnosis, I was happily immersed in a satisfying career as a clinical anesthesiologist and department chair. Then came the news that Maria, at the time only 40 years old, had triple-negative breast cancer. My controlled world turned into one of emotional upheaval driven by my care and concern for her well-being. Throughout her years of seeking treatments that might stem the disease, she and her family had intermittently lived with me and my husband and our three sons. On one occasion, Maria participated in a clinical trial that was administered through a cancer center near our home. Although I loved having Maria close by, I felt her anxiety and witnessed her struggle each time I accompanied her to medical appointments or chemotherapy infusions. I became increasingly stressed by and frustrated with my inability to make her better.

As many of us know, the interventions we put our patients through can be worse than their disease. Maria underwent mastectomy and reconstructive surgeries and had been receiving chemotherapy for about a year when my cancer diagnosis required me to share that misery.

Chemotherapy is evil. Maria and I called Adriamycin the "red devil." Maria's stomach proved tougher than mine. I became so ill that every time I received the drug I developed anticipatory nausea; I would retch as soon as my port was disinfected with alcohol. Can you imagine an anesthesiologist troubled by the smell of an alcohol wipe?

The red devil worked for me. It didn't work for Maria. Another chemotherapy drug, Taxotere, caused her severe, searing bone pain. She would go on to suffer three additional chemotherapeutic agents, including those she received during her participation in the PARP inhibitor trial. For that trial, Maria had initially been randomized out of the treatment, but then was given the experimental treatment as compassionate care. It was during that regimen that we learned she had not responded; the cancer had been found in her brain, her lungs, and her liver.

Healing Oneself

Physicians can become annoyed by, and critical of, seemingly needy patients and their families. Not only did I need to deal with my own emotions while watching my sister wither away, I also acted as go-between with my family. This meant that each day during Maria's illness, my father would ask me the same question, "Maria is going to be all right, isn't she?" One day, I just could not bear the burden of his sadness anymore. I blurted, "Dad, stop asking me a question you know the answer to. Do you want me to lie to you?" The look on my father's face caused me to immediately regret my harsh response. Now, when patients and families press me for answers to difficult questions, I remember the expression on his face that day, and I strive to be as compassionate as possible.

Chronic neuropathic pain leaves the best of us open to depression—and opiate dependency. My husband, a practicing neonatologist, was no exception. The central C5-C6 cord injury that Brian sustained four months before Maria died had initially resulted in full quadriplegia. Over time, however, he was fortunate enough to regain his ability to walk and the partial use of his arms and hands. Unfortunately, he also suffered spasticity and neuropathic pain. Brian came home from his eight-week rehabilitation stay with a dependence on oxycontin. His mood was often dark as he mourned the loss of his career and the use of his hands. Even my work with patients in my chronic pain practice did not prepare me for what he faced following his injury.

Hospitalization and an addiction specialist helped wean him from oxycontin. His spasticity and pain, however, will remain a lifetime challenge. Realizing this, I have learned to be much more aware of his daily ups and downs. Most days we joke, and I try to keep things light. But Brian's frustration can easily ignite when I need to assist him with simple tasks, such as tying his tie, buttoning his shirt, or changing a lightbulb, or whenever he mourns the loss of his career. We are well aware that going forward, each day will test us.

My family and I were at my sister's side when she passed away in February 2011. As an anesthesiologist, I typically don't see death in this way. I am now, however, acutely aware that every time I anesthetize a patient, I hold a precious life in my hands. This realization has, I think, made me a better physician. I only wish the cost of this lesson had not been so enormous. ■

Rosalie Tocco-Bradley '88 is regional chair and medical director of the Department of Anesthesiology and Pain Medicine for St. Joseph Mercy Health System (CHE-Trinity Healthcare); chief clinical officer of Anesthesia Associates of Ann Arbor; and a member of the Michigan Board of Medicine.

This essay was adapted from "Becoming a Better Physician ... at a Cost," ASA Newsletter 78(7): 33-34 of the American Society of Anesthesiologists. A copy of that text can be obtained from ASA, 520 N. Northwest Highway, Park Ridge, IL 60069-2573.

TO TOC (OPPOSITE PAGE)

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BACKSTORY

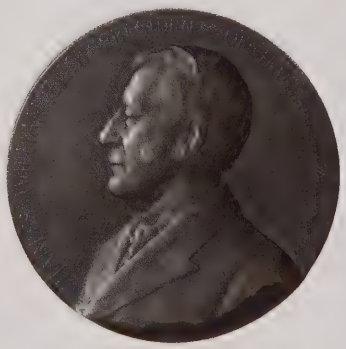
FROM THE COLLECTIONS AT HARVARD MEDICAL SCHOOL

"MEDICINE is an intensely practical calling."

So said Frederick Cheever Shattuck, Class of 1873, at dedication ceremonies in June 1906 for five new HMS buildings. Those Beaux-Arts buildings, still bordering the Quad, were designed to satisfy a practical mission: to upgrade the School's environment for research and education. But of equal moment was the philosophical conviction that these buildings were, as J. Collins Warren, Class of 1866, Moseley Professor of Surgery, noted, "to be made an agent not only for the diffusion of learning, but for substantial aid and comfort to the suffering."

At the time, the School had revised its curriculum to place a greater emphasis on laboratory work; the buildings were considered emblematic of a new start for medical education and research in this country. HMS Dean William Lambert Richardson said that "the facilities [were] so ample and the equipment so complete that the Faculty has decided to ... open all courses, including laboratory courses, to persons not candidates for the degree of Doctor of Medicine."

—Susan Karcz



FORMING FUNCTION: Architect's model and drawings, circa 1903, of the proposed Quad buildings (top, and bottom, far left) and design for unrealized gates to the Quad (left). Above, a bronze medal, designed by French artisan Leon Deschamps, depicts Charles William Eliot, president of Harvard University at the time of the Quad's dedication; the obverse shows the Johnson Gate in Harvard Yard. Eliot spoke on the future of medicine at the Quad's dedication ceremonies. A model of a hospital ventilation testing device (middle, far left), also known as an anemometer, that was owned and used by Morrill Wyman, HMS Class of 1837, who studied and wrote about the mechanics and health benefits of proper air movement and ventilation in hospitals and sickrooms; and the ceremonial trowel used to lay the cornerstone of the Francis A. Countway Library of Medicine on May 12, 1964.

Model, drawings, and trowel courtesy of the archives of Harvard Medical School; medal courtesy of the Storer Memorial Collection of Medical Medals in the Boston Medical Library; anemometer courtesy of the Warren Anatomical Museum at the Francis A. Countway Library of Medicine.

FIVE QUESTIONS

FOR NANCY TARBELL

Dean for Academic and Clinical Affairs, Harvard Medical School

The C. C. Wang Professor of Radiation Oncology, Massachusetts General Hospital

Head, Pediatric Radiation Oncology, Mass General

What attracted you to pediatric oncology?
The magical idea of curing cancer in children. I was ten years into this career path when the role of the pediatric oncologist changed to one that emphasized calibrating radiation therapy to reduce side effects without decreasing the cure rate. Now the focus is on survivorship and quality of life. The improved survival rates we now see are an outgrowth of our success with treatment, giving us the opportunity to focus on survivorship, in particular how to manage side effects of treatment.

Why did you become involved in faculty development?
I thought I could have a greater, though indirect, impact on patient care by serving as a mentor and a source of career guidance to the next generation of clinicians. I also became more involved in the recruitment and retention of faculty. I wanted to make sure there were support systems in place, whether those systems included centralized faculty development programs or hospital- or department-based programs.

Why is mentoring so important to you?
I'm giving back something that was given to me. I applied to medical school because a college friend urged me to do so. She saw something in me that I didn't know was there. There was little mentoring when I went to medical school. Some teachers were inspirational but that was not the same as the way we view mentoring now.

How do you switch gears from Dean Tarbell to Dr. Tarbell?
I love that I still am able to take care of patients. The clinical work keeps me grounded, in tune with what the faculty are experiencing and how medicine is changing.

When I put on that white coat every Wednesday, I know that on that day I'm going to be a doctor. And I know how to do that. For me, clinical work remains rewarding.

Okay, the elephant in the room. How do you think women are faring in medicine?
Women are still expected to behave in ways different from those expected of men. Men can say things, which, if said by a woman, would be considered too aggressive. We all have gender stereotypes, men and women alike. They're part of who we are, and they don't change quickly.

It would be great to feel as though we could break down some of the challenges that remain for women, ones that are subtler and a little bit harder to get at. I would love to look back, and say that, actually, we don't need to talk about gender anymore. —*Susan Karcz*

JOHN SOARES

HARVARD MEDICAL SCHOOL
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M1523

*Graduates from the last five years are offered a special membership to the prestigious Dean's Council when they give $100+ for each year since graduation

DO NOT WRITE BELOW THIS LINE

President's Report

The first meeting of the 2014–15 Alumni Council took place in October. Among the many items discussed were ideas for enhancing communication between HMS and its graduates. One way this could happen on a local level would be through small informal wine and cheese events. Five pilot events have been scheduled already. Please write to me if you are interested in hosting one in your area.

A second item involved planning for the seventy-fifth anniversary of women being accepted as students at HMS. We hope that all graduates, but especially all female graduates, will be engaged in activities celebrating this milestone. Stay tuned!

The council also heard from Rick Shea, associate dean for campus planning and facilities, about a proposed redevelopment of the Longwood campus. Everything is being looked at carefully, with an eye to the future needs of research and education at HMS.

Barbara McNeil '66 is the Ridley Watts Professor of Health Care Policy at HMS, founding head of the School's Department of Health Care Policy, and a professor of radiology at Brigham and Women's Hospital.

TAKING THE LONG VIEW

Years of dedicated pursuit brings insights into the cell cycle and cancer


Randy King

FIFTEEN YEARS AGO, chemical genetics was a young discipline. Before the discovery of RNA interference transformed nature's gene silencer into a routine lab tool, scientists seeking to explore cellular mechanisms at the molecular level relied on other methods: they amassed cells in arrays, exposed them to interesting chemical compounds, and waited to see what happened.

Randall King '97, the Harry C. McKenzie Professor of Cell Biology at HMS, knows well what it means to invest time in discovery. He studies the cell cycle: how it works and what goes wrong in disease. In 1999, in one of the first assays undertaken at the Institute of Chemistry and Cell Biology–Longwood Screening Facility, King's team turned up some promising chemical leads. Pursuing those leads has kept them busy for more than a decade.

That assay found several chemicals that inhibited the cell cycle, the process by which a cell duplicates and then divides to form daughter cells. When working properly, cell division ensures healthy growth. When running out of control, defects in the process can result in cancer. In 2004, the group reported in *Science* that one chemical, ubistatin, blocked cell division by inhibiting the cell's protein elimination system.

Learning how cancerous growth might be stemmed is central to King's research, so two other chemicals that also influenced cell division piqued his interest. In 2010 King and his colleagues published a paper in *Cancer Cell* that detailed how one of those inhibitors, tosyl-L-arginine methyl ester, delays the cell cycle briefly. In a 2014 *Nature* paper, his team described how another compound, apcin, briefly delays mitosis, the phase of the cell cycle in which chromosomes are duplicated and distributed to daughter cells. When working together, however, the two inhibitors slow mitosis to a crawl. The cell in fact dies without completing the mitotic process.

"Having these chemical tools, we can screen cancer cells and ask if there are different cell lines that are particularly sensitive to this type of intervention," King says.

While the chemical compounds that proved interesting in that 1999 screen might one day be developed into drugs, those findings of 15 years ago are prized primarily because they answered fundamental questions about the inner workings of cells, insights that will be crucial to the success of any future therapeutic. Patience, insight, focus: the stuff of discovery-based research.

—*Elizabeth Cooney*


Robert Coughlin

RAINBOW BRIDGE

LGBT community gathers for advisory committee's inaugural reception

WEARING A BRIGHT rainbow-colored lei over his crisp, collared shirt, Robert Coughlin was one of the nearly one hundred people who circulated in the lobby of the Joseph B. Martin Conference Center, shaking hands with old colleagues and new acquaintances.

Coughlin, the HMS director of financial aid, is a co-chair of the newly formed LGBT Advisory Committee at Harvard Medical School and the Harvard School of Dental Medicine. The September 30, 2014, event that brought so many together marked the introduction of the advisory committee for the LGBT (lesbian, gay, bisexual, and transgender) Office at HMS.

"There are many of you with us today who have worked tirelessly to provide health care, conduct research, and advocate for the well-being of our richly pluralistic world, and I thank you for all that you have done," said Jeffrey S. Flier, HMS dean, at the gathering. "I'm proud to see this diversity in our LGBT staff, students, faculty, and trainees."

Flier was joined in addressing the crowd by Bruce Donoff '73, dean of HSDM; Alvin Poussaint, HMS faculty associate dean for student affairs; and the co-chairs of the LGBT advisory committee, Coughlin and Mark Schuster '87, the William Berenberg Professor of Pediatrics at HMS and chief of general pediatrics at Boston Children's Hospital.

The recently established LGBT office will be headed by program manager Jessica Halem, who will help the committee identify concerns, needs, and resources across the LGBT community at HMS and HSDM. She will also work with Harvard University and affiliated hospitals to advance the LGBT agenda.

Said Halem, "Housing the LGBT office inside the Office for Diversity Inclusion and Community Partnership—an office that has for years been working on issues of people of color and historically underrepresented individuals at HMS—puts us inside the mix, where we can support people in bringing all of their identities to the table."

Joan Reede, dean for diversity and community partnership, who leads the DICP, said she is pleased that LGBT work will fall within her team.

"Diversity inclusion means everyone," said Reede. "It's really recognizing that it's the entire community that makes HMS successful."

An important aspect of the LGBT Advisory Committee is that faculty and staff will work alongside students and trainees as part of the new initiative.

Cary Crall '16, an advisory committee member and HMS student, thinks the advisory committee will help encourage involvement from LGBT students, and will highlight LGBT research pursuits and clinical interests as an area of focus for medical education and advancement.

—Angela Alberti

CLASS NOTES

NEWS FROM ALUMNI

1945 70th REUNION

Robert Post

I played the role of Elwood P. Dowd in a script-in-hand production of *Harvey*.

1955 60th REUNION

David Nathan

I was recently honored as the inaugural recipient of Boston Children's Hospital Lifetime Impact Award. There was something very special about being recognized by my colleagues, many of whom I enjoyed mentoring as they launched their own distinguished careers. I am proud to have served as president of Dana-Farber Cancer Institute and as physician-in-chief at Boston Children's and not only to have helped develop the pediatric hematology/oncology program at Dana-Farber/Boston Children's Cancer and Blood Disorders Center, but also to have witnessed it become one of the nation's premier programs.

1958

Anita Herald

This was a banner year for me! My two granddaughters both graduated from college—Rachel from the Air Force Academy and Amber from Miami University in Ohio.

John Livingstone

I am writing a textbook for physicians and nurses on relational science in health-behavior change and shared decision making. This has been a big challenge, yet is the most exciting project of my career.

I am also conducting workshops for rowers and rowing coaches at Craftsbury Rowing Center in Vermont and at the Institute for Rowing Leadership in Boston using a program called the Rowers Mind-Body Routine. It is exciting work, and athletes and coaches are receptive to new ways to cope with emotions and thoughts that show up in the mind and body during training and competition.

At age 81, I am rowing regularly, in addition to maintaining a private practice with my wife, Joanne, who is also a psychotherapist. We live in Provincetown, Massachusetts. People ask when am I going to retire, and I answer, "I am retired—I swim or row every day."

1962

Edward Silberstein

I am still working on better ways to treat thyroid cancer. I have volunteered as an assistant curator for two recent exhibit catalogs, one for a Monet in Giverny exhibit and another on Cezanne's still lifes. The Monet catalog is now part of the Bibliothèque Nationale collections in Paris, and the Cezanne exhibit was presented at the Barnes in Philadelphia. Both projects were great fun.

1966

Eugene Appel

Life in Southern California is good, and I am enjoying retirement in the sun.

Mahlon DeLong

I was pleased to accept the 2014 Lasker-DeBakey Clinical Medical Research Award along with Alim Benabid for the development of deep-brain stimulation of the subthalamic nucleus, a surgical technique that reduces tremors and restores motor function in patients with advanced Parkinson's disease. Specifically, I formulated a new model for the brain's circuitry and exposed a fresh target for treating this illness.

Joel Friedman

Carol and I have just celebrated our 50th wedding anniversary. We were pleased that **Scott Nelson** could attend the celebration along with other close friends, our children, and our five grandchildren. I've completed my second year of retirement and am enjoying this new chapter of my life very much. I teach in the Practice of Medicine course at Stanford, attend a weekly cardiovascular conference there, and do some utilization review work for the California State Fund in order to keep my hand in medicine. I work out at the YMCA regularly and play golf two to three times a week. My biggest challenge has been beginning piano lessons! I love this, but I don't plan on performing at Carnegie Hall.

CLASS NOTES

NEWS FROM ALUMNI

David Gilmour

I am retired and leading bike tours with a little company in Vermont. I work for tips, perhaps a first for an HMS grad! It does keep me fit.

Charles Hatem

After 44 years of practicing primary care and teaching at Mount Auburn Hospital in Cambridge, Massachusetts, I'll be stepping down next June.

Jay Kaufman

I retired from the practice of ophthalmology two years ago and have had a nearly seamless transition to retirement. I have been studying Spanish, taking courses at Harvard, and trying desperately to lower my golf handicap. I have just published my first children's book, *The Mystery of the Cliff House*, meant for middle-school readers. It is probably below the reading level of all of our classmates except **Eugene Appel**.

Ross Neisuler

My wife, whom I courted while I lived at Vanderbilt Hall, and I have been enjoying our retirement. Our sons have grown and each is a parent twice over. We live in Newton, Massachusetts, and have thrown ourselves into a whirlwind of activities, especially the Harvard Institute for Learning in Retirement, a peer-taught learning community that's almost like being back on a liberal arts campus. We see **Phil Stubblefield** and his family frequently.

Scott Haviland Nelson

I'm still practicing psychiatry on an Indian reservation in rural New Mexico. I've offered to sponsor an open house sometime soon for all HMS grads who live in or reasonably near Santa Fe. Expect to hear from me or the alumni office.

Robert Owen

I retired from my full-time staff position at the San Francisco VA but continue to work there two days a week running the environmental medicine program and directing the fourth-year University of California San Francisco School of Medicine gastroenterology elective. I remain active as a professor of medicine, epidemiology, and biostatistics at UCSF, teaching GI histology and physical diagnosis.

In November, **Joel Friedman**, **Jane Marmor**, **Mike Marmor**, and I attended the Breakthrough Prize in the Life Sciences Symposium at Stanford, where **Mahlon DeLong**, one of last year's Breakthrough winners, presented an address on future directions for understanding brain function, disorders, and treatment.

Theodore Pincus

I am based at the Rush University Medical Center in Chicago. Thirty-six years ago, I observed that poor functional status, as measured on a patient questionnaire, provides a far more significant reversible risk factor for premature mortality in rheumatoid arthritis—and probably in many diseases—than do lab tests or imaging data. I am currently investigating whether this observation may apply to Parkinson's disease. My daughter, **Laura '03**, is a dermatopathologist at the University of San Francisco.

Anne Rassiga

I'm still living in a small town and pleased to have been able to develop a rural cancer center here with three great colleagues. However, with changes in health care models and a new CEO appointment in the works, this very small rural hospital is becoming even smaller. Everything seems so uncertain. Retirement looks more and more attractive! But the new developments and drugs in oncology are so exciting that medicine remains stimulating.

Kent Ravenscroft, Jr.

My wife, Patti, and I have been living in Paris seven months a year

for eight years now. I still have one psychiatric patient, a globetrotter like us, who is doing international climate change work. I have been making sculpture for the past four years, and of course, have been enjoying great food and culture. Patti runs a culinary and cultural tours business for small groups traveling to sites throughout France, as well as in Morocco, Vietnam, and Italy. Come join us, or visit us at some point this year; it may be our last in Paris.

Stephen Schoenbaum

I work part-time at the Macy Foundation in New York.

David Howe Wegman

After retiring from full-time academic work in 2010, I'm now leading a study with colleagues at research institutions, government agencies, and nongovernmental organizations around the world to try to solve the problem in Central America of epidemic chronic kidney disease of nontraditional origin. I am also working as one of three directors of the Alpha Foundation for the Improvement of Mine Safety and Health, which awards grants for research to protect miners; teaching one class a year at the Harvard School of Public Health; serving as a consultant to the Massachusetts Department of Public Health; and working on several activities for National Academy of Sciences and Institute of Medicine committees. I was recently in Armenia working to develop collaborations in occupational and environmental health. But I'm retired!

Bruce Weintraub

In my 26 years as a branch chief at NIH and the first director of its endocrine training program, I built an extensive patent portfolio. One patent was for the invention of recombinant thyroid-stimulating hormone used in the diagnosis and treatment of thyroid cancer. This was licensed to Genzyme under the name Thyrogen, and was approved by the FDA in 1998. With the success of this drug and the biotech experience I gained as it was under development, I was able to co-found a startup company in Rockville, Maryland, in 2001. The company is doing very well and has a large portfolio of human and animal recombinant second generation "designer" analogs and has many agreements pending with large pharmaceutical firms. I love my life as a biotech entrepreneur and have no plans to retire. What varied paths we've all taken!

1967

Oluwatope Mabogunje

I retired from surgical practice at the Dayton VA Medical Center in January 2014. I hope to do some traveling to distant parts of the world.

1968

Sarah Donaldson

This past summer I was honored with a Radiology Leadership Institute Luminary Award, presented to radiologists who possess exceptional experience and demonstrate an unusually high level of leadership in organized radiology. I currently hold the Catharine and Howard Avery Professorship at Stanford University School of Medicine.

1969

Elizabeth Thomas Anderson Mayer

So sorry to have missed our 45th. I'm still enjoying retirement, doing a little teaching for the University of California Berkeley-University of California San Francisco Joint Medical Program, biking, gardening, and helping care for my new granddaughter, Dorothea.

1977

Francis Lonergan

After 30 years of mostly solo family practice in a small community outside of Fort Worth, Texas, I decided to take a different road. I'm now the medical director of a clinic for the homeless in Fort Worth. I have an assistant professor appointment at the University of North Texas Health Science Center. But the bulk of my work is at the clinic, where I'm the only medical provider. I work with a great group of people, including an outreach team that goes into shelters to extend the services of the clinic. We are trying to develop a more comprehensive health care system for the home-

CLASS NOTES

NEWS FROM ALUMNI

less based on the medical home and chronic illness models. We have also recently moved into a building shared with the local mental health provider and are developing an integrated mental health and primary care program, the first in this part of Texas. It's really exciting work, and I feel amazingly blessed to have come upon it at this stage of my career. Meanwhile, my wife is re-creating herself as an artist and writer, and our adolescent son is doing well maneuvering the complexities of sophomore year in high school. Life is good. Best to all.

1980 35th REUNION

John R. Adler, Jr.

I have been busy for the past few years creating a new-generation journal for all medical specialties called *Cureus* (pronounced as "curious"). It's open access and free. Please consider publishing your own paper in *Cureus* soon. In this journal even the simple case report can become a widely read thing of beauty.

1990 25th REUNION

Leigh Kimberg

What a year! My fiancée of 25 years, Melissa Lim, and I got married and celebrated with our two children, family, and friends. We sent our son, Sam, off to college at Columbia and feel grateful to still have our daughter, Abby, a junior in high school, home with us. After 20 years of practicing primary care in a San Francisco Department of Public Health community health center, I took a new job at the University of California San Francisco as director of the program in medical education for the urban underserved. This five-year program prepares students to be leaders in the care of underserved communities. I continue to do intimate partner and family violence prevention work on behalf of the SFDPH. I feel lucky to have such inspiring work!

1992

Theodore Schwartz

I am excited to announce that I have been named the David and Ursel Barnes Professor of Minimally Invasive Neurosurgery, the first endowed professorship in neurosurgery at Weill Cornell Medical College.

1997

Steven Kalkanis

I was appointed chair of the Department of Neurosurgery and co-director of the Neuroscience Institute at the Henry Ford Hospital in Detroit. I will remain the medical director of the Center for Cancer Surgery at the hospital.

Randall King

I was honored to be named one of the recipients of the 2014 Alpha Omega Alpha Robert J. Glaser Distinguished Teacher Award. This award recognizes my work in helping to develop a postdoctoral training program for scientists in education, in establishing patient clinics to integrate basic science with clinical medicine, and in helping to plan a curriculum redesign for the HMS MD program.

2001

Shireen Donaldson-Ramos

I received the Dr. Melville G. Magida Award from the Fairfield County Medical Association and the Rosenthal Family Foundation. The award recognizes a physician age 39 or younger who has shown a notable ability for patient treatment and care, and a sensitivity to patient-physician relationships.

Share Your News

If you have updates you'd like to share in Class Notes, you can submit them easily and securely to classnotes@hms.harvard.edu. Be sure to include your full name and class year.

JAKE MILLER

OBITUARIES

REMEMBERING DISTINGUISHED LIVES

1940s

1940

William A. Dafoe
November 21, 2014

1942

J. Bradford Millet
August 30, 2014

1943

Harold Brown
August 14, 2014

Albert B. Ferguson, Jr.
August 20, 2014

Stanley L. Lee
July 27, 2014

Winsor C. Schmidt
July 24, 2014

Louis E. Ward
October 17, 2014

1946

Wallace F. Haley, Jr.
September 3, 2014

1949

Waddell Barnes
October 7, 2014

Thomas C. Hall
September 2014

Henry S. Harvey
June 14, 2014

1950s

1951

Mohammad Atik
June 5, 2014

John L. Fahey
August 19, 2014

Wilbur H. Lyon, Jr.
August 19, 2014

1952

Craig B. Leman
July 13, 2014

John A. Malcolm
July 21, 2014

Hollis J. Wiseman
October 28, 2014

1953

James W. Forrester
August 7, 2014

Alvin Kahn
October 2, 2014

1954

John C. Norman, Jr.
July 23, 2014

Dorothee L. Perloff
November 2, 2014

1955

John E. Leigh
August 14, 2014

1956

Chase N. Peterson
September 16, 2014

1958

Hugh P. Chandler
October 9, 2014

Edward M. Haley
August 12, 2014

Stephen L. Wangensteen
December 1, 2014

1960s

1960

Charles S. LaMonte
June 24, 2014

1961

Elwin E. Fraley
July 31, 2014

Mark R. Hanschka
June 1, 2014

1962

Peter A. Evans
November 30, 2014

1963

Frederick L. Moolten
October 29, 2014

1965

Martin F. Kagnoff
November 16, 2014

1966

Donald E. Loew
July 23, 2014

1970s

1972

Charles T. Levitan
September 10, 2014

Eileen R. Toth
October 18, 2014

1975

Roy M. Rubin
June 29, 2014

1979

Allison J. Doupe
October 27, 2014

1980s

1983

Peter R. Baginsky
November 14, 2014

This listing of deceased alumni includes those alumni whose notices of death were received between July 26, 2014, and December 12, 2014. Links to full obituaries of these alumni can be found at hms.harvard.edu/memoriam.

If you know of an HMS alumna/us who has died recently, please send an email with the link to the obituary to hmsalum@hms.harvard.edu.

TAKING A HISTORY

PROFILE OF JOAQUÍN CIGARROA, JR.

CLAIMS TO FAME
Internal medicine physician, Laredo Medical Center; former member of the Texas Higher Education Coordinating Board; former member, MD Anderson Cancer Center Board of Visitors

THE PERSONAL TOUCH
Continuity and personal relationships are hallmarks of the care Joaquín Cigarroa, Jr. '47 provides. This nonagenarian still practices medicine 12 hours a day, often making house calls. "If patients are unable to come to your office, then I think that you should go to their homes," he says. Unhurried communication with patients, families, and other physicians, says Cigarroa, is the foundation of good medicine.

EXTENDED FAMILY
In the 1930s, Cigarroa's father, a physician, set up a general medical practice in the fast-growing border town of Laredo, Texas. By age eight, Cigarroa was accompanying his father to work, and at age ten, witnessed his first surgery. "It was an operation to remove an ice pick from the heart," Cigarroa says. His father explained each step in the procedure. "I saw him practice medicine not as a business, but as a person. He treated his patients as if they were family."

FIRST PRINCIPLES
Cigarroa spent his summers in Mexico City with his extended family, many of whom were involved in education and teaching. "I got to see what education meant to a person's life," he says. The prospect of applying his mind—and his heart—to medicine took hold. In 1943, a telegram granted young Cigarroa's wish—he had been accepted to HMS. He remembers two things from his first day: the gloominess of the New England December day and the first words of his anatomy professor, Robert Green. "He began by saying, 'Gentlemen, respect the cadaver. It was once the abode of the human soul.'" Cigarroa was taught by William Castle, Class of 1921; Francis Peabody, Class of 1907; and George Minot, Class of 1912; among others. Each conveyed the importance of respecting the patient, listening carefully, and observing well in clinic. "I follow those principles," he says.

THE PULL OF HOME
Cigarroa completed internships at the University of Chicago and the former Boston City Hospital before serving in the Korean War in a special unit researching hepatitis. His heart, however, remained in clinical care. "When I left Laredo, I left with the intention of coming back," he says. He established an internal medicine practice there and, in 1954, met and married Barbara, his wife of 60 years.

A BEAUTIFUL MIND
Cigarroa has been a driving force in medicine and education in Texas, having helped establish several medical centers and serving as chief of medicine at the Laredo Medical Center. He has also helped recruit doctors to an area that previously was underserved by physicians. As a testament to Cigarroa's commitment to education, his ten children have earned a combined 22 degrees from Ivy League schools, including two who graduated from HMS. "There's nothing more beautiful than learning," he says.

—Angela Alberti

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